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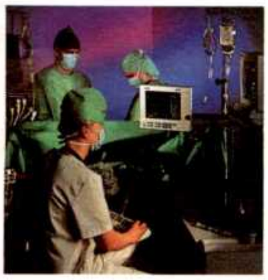

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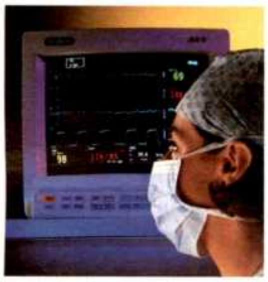

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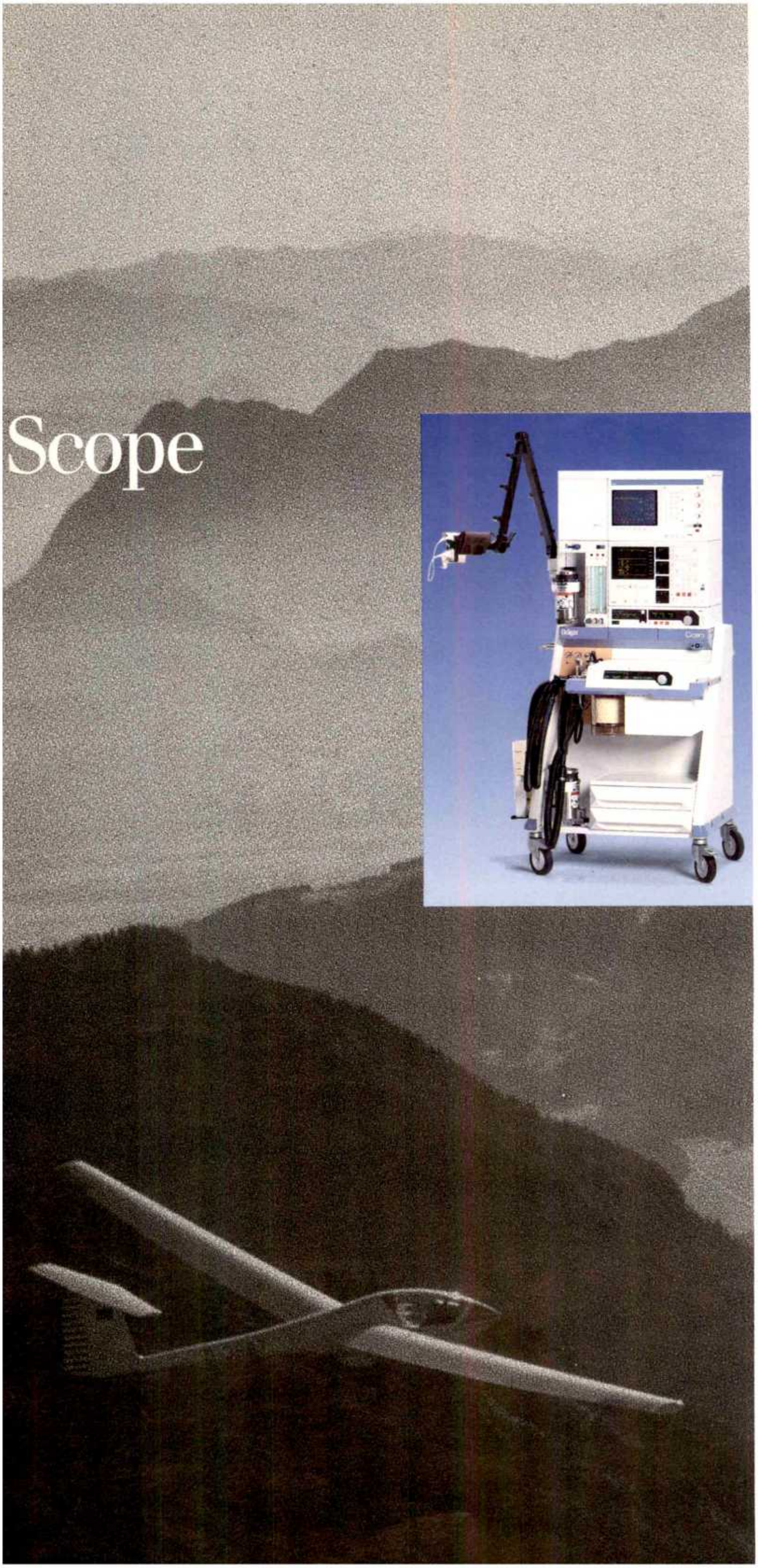

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Handbook of British Anaesthesia 1993/4

This Handbook *is produced by the Editorial Board of* British Journal of Anaesthesia

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ABBREVIATED PRESCRIBING INFORMATION: TORADOL* for intramuscular injection 30mg/ml. TORADOL* for oral administration 10mg tablet. Please refer to both data sheets before prescribing. **USES: Intramuscular injection** - relief of pain associated with surgical procedures. **Oral tablets** - short-term management of moderate pain associated with surgical procedures. **DOSAGE: Intramuscular injection** *Adults:* Initially 30mg im followed by 10 to 30mg im every 4-6 hours as required. A total daily dose greater than 120mg is not recommended. In the initial postoperative period, TORADOL may be given as often as every 2 hours if required. Continuous im usage should not exceed 5 days. *Elderly:* A lower total daily dose is recommended. **Oral tablets** *Adults:* 10mg every 4-6 hours as required. Doses exceeding 40mg per day are not recommended. Intended for short-term use only (up to 7 days). *Elderly:* A longer dosing interval, e.g 6-8 hourly may be advisable. **Intramuscular injection and oral tablets** For patients who have received parenteral TORADOL and are converted to oral tablets, a total combined daily dose of all forms should not exceed 120mg on the day the change of formulation is made. Not recommended for children under 16 years. Reduce daily dose in renal impairment. Opiate analgesics may be used concomitantly if required. The following information refers to both the intramuscular and oral dosage forms: **CONTRA-INDICATIONS:** History of peptic ulcer; coagulation disorders; hypersensitivity to ketorolac trometamol; NSAID-induced allergy; treatment with lithium salts; asthma; severe renal insufficiency. **WARNINGS AND PRECAUTIONS:** Use with care in the elderly, in patients with a history of GI disease, those with cardiac, renal, hepatic or allergic disease, hypertension, those who are hypovolaemic and those taking diuretics. NSAIDs have been associated with renal disease. Fluid retention may occur. TORADOL inhibits platelet aggregation and may prolong bleeding time. Caution is advised where strict haemostasis is critical. Prothrombin time should be monitored in patients receiving oral anticoagulants. Renal clearance of ketorolac is decreased by probenecid. NSAIDs decrease renal clearance of methotrexate. TORADOL reduces the diuretic response to frusemide. Concomitant use of other NSAIDs is not recommended. Not recommended in pregnancy/labour or in breast-feeding women. **SIDE-EFFECTS:** (see data sheets) *GI:* Nausea, vomiting, dyspepsia, diarrhoea, peptic ulcer, haemorrhage, perforation, constipation. *CNS:* Drowsiness, dizziness, headache, convulsions. *Renal:* Acute renal failure, flank pain, haematuria, raised blood urea. *Other:* Hypersensitivity reactions (anaphylaxis, bronchospasm, laryngeal oedema, hypotension, flushing, rash), purpura, oedema, abnormal liver function tests, postoperative wound haemorrhage. Injection site pain has occurred following administration of the intramuscular injection. **PRESENTATION:** TORADOL intramuscular injection: Single-dose ampoules containing ketorolac trometamol 30mg, ethanol, sodium chloride and water in a 1ml solution. (PL 0286/0111, 10 ampoules £13.14). TORADOL tablets: White/creamy-white round film-coated tablet, each containing ketorolac trometamol 10mg. (PL 0286/0125, 100 tablets £33.43). Further information is available on request from: Syntex Pharmaceuticals Limited, Syntex House, St. Ives Road, Maidenhead, Berkshire. SL6 1RD. *TORADOL is a trademark. **References: 1.** O'Hara DA, Fragen RJ, Kinzer M, Pemberton D. Clin Pharmacol Ther 1987; 41: 556-61.

SYNTEX

Introduction to the *Handbook of British Anaesthesia 1993/4*

The *Handbook of British Anaesthesia* has now reached its sixth edition, and, as with its predecessors, is produced by the Board of *British Journal of Anaesthesia*. We have kept much of the successful format of the previous edition, with the inclusion of information about the activities and meetings of both National and International Anaesthetic Societies.

The international aspects of anaesthetic practice are becoming ever more important, as the growth of research and clinical practice now depends much more on international developments and collaboration for both pharmaceutical and equipment innovations. At the same time, many anaesthetists see increasing opportunities for studying overseas, and there is therefore a need to address the issues of the comparative equivalence of basic anaesthetic training programmes and specialist certification. Thus, the editors have retained the present guides to both Basic and Higher Specialist Training in the U.K. in the hope that it may help both our own trainees and those coming to the U.K. from overseas.

The Calendar of Major Anaesthetic Events aims to highlight the major National and International meetings and courses during the coming year; its success depends on the Secretaries of the various Specialist Societies and Congresses liaising with the Journal.

The list of Useful Addresses has also been expanded, again with an increasing international flavour, to include the addresses of the major International Anaesthetic Societies, and the Editors of the other international anaesthetic journals.

We hope that there are few major errors in this *Handbook*; we depend on our readers to keep us up to date of any important changes of fact or circumstance: these will be included in the next edition, which is already planned for 1994.

The Board of *British Journal of Anaesthesia* is grateful to those who have helped to produce this *Handbook*, particularly the Secretaries of the Specialist Societies, the Heads of Academic Departments, the Regional Educational Advisers, and other anaesthetic bodies. The cost of this publication has been partly defrayed by contributions from our colleagues in the Pharmaceutical Industry and Equipment Manufacturers; we thank them. The Editors of the *Handbook* also acknowledge the contributions of the Journal's Technical Editor, Ms Linda Gough and Miss Karen Marden.

G. Smith and J. W. Sear
Editors

British Journal of Anaesthesia

British Journal of Anaesthesia, the second oldest anaesthetic journal in the world, was founded in 1923, the year after the launch of *Anesthesia and Analgesia, Current Researches*. The Journal remained the largest independent journal of anaesthesia in the world until January 1990 when a formal link was established between the Journal and the Royal College of Anaesthetists. This formal link, however, has not affected the independence of the Editorial Board. The Journal is governed by an Editorial Board which elects its members according to a constitution formulated in accordance with the laws governing charitable institutions within the U.K. Through the medium of three elected trustees, the Board effectively owns the Journal and the constitution is such that the major, indeed only, role of the Journal is to provide a medium for dissemination of scientific and education communications in anaesthetic and related fields.

The Royal College has now become responsible for ratifying the appointment of Members of the Board which continues to function as before and the President and Vice-President of the Royal College are *ex officio* Members of the Board. The Board acts independently to elect the Editors and Assistant Editors and regulate the normal business activity of the Journal.

In the early 1950s, the Journal began to carry "educational papers", dealing mainly with physics and electronics, and in 1964, on the initiative of A. R. Hunter, launched symposium (later called postgraduate) issues. Initially, these were published twice yearly, usually January and July, but in 1987 the Board agreed that only one issue per annum would be devoted to a symposium issue and that an attempt would be made to carry an invited review article in every general issue of the Journal.

The Journal is registered as a charity under U.K. law and any profits must therefore be directed properly into educational activities. Whilst the principal activity is, of course, publication of the Journal, the Board has in addition:

(1) Arranged annual writing workshops for doctors in training as well as organizing symposia on scientific paper writing at international congresses.
(2) Furnished the *British Journal of Anaesthesia* library at the Headquarters at the Association of Anaesthetists in London.
(3) Donated to the lecturer fund established in the memory of the late Gordon McDowall.
(4) Established *British Journal of Anaesthesia* Research Fellowships since 1987. Currently, the Journal supports two such Research Fellowships at any one time.
(5) Established in 1988, short-term travelling fellowships to enable young anaesthetists from other countries to visit selected training centres in the U.K.

The following is a list of Postgraduate Educational Symposia published in recent years.

1985:	January	Brain ischaemia—its prevention and treatment
	July	Anaesthetic equipment
1986:	February	Aspects of intensive care
	July	Local anaesthesia
1987:	January	Adverse effects of drugs used in anaesthesia
	July	Complications and medico-legal aspects of anaesthesia
1988:	July	Anaesthesia and myocardial ischaemia
1989:	August	Aspects of pain
1990:	July	The lung
1991:	August	Fluid and electrolytes
1993:	August	Receptors and transmembrane signalling: cellular and molecular aspects of anaesthesia

MAKE-UP OF THE JOURNAL

Each general issue of the Journal comprises usually the following:

EDITORIAL

This is always invited and freely submitted material is not accepted for publication.

ORIGINAL ARTICLES

This section contains original papers covering both experimental and clinical research. Papers of a basic physiological or pharmacological nature are acceptable providing they are of some relevance to anaesthesia.

REVIEWS

The majority of review articles are commissioned by the Editor of Education Reviews. However, a small number of freely submitted review articles which appear interesting, authoritative and well-written, may be accepted after undergoing peer review.

SHORT COMMUNICATIONS

Authors are encouraged to submit original material under this heading. The size of such papers should be no more than 1200–1500 words, and the paper should contain not more than 1 table or figure and not more than 6 references. Such manuscripts are divided into a summary, introduction, methods and results, and comments sections.

CASE REPORTS

British Journal of Anaesthesia welcomes particularly submission of case reports but authors should be aware that simple description of anaesthetic management of a particularly difficult case may not warrant publication. Case reports should carry a new or original message or should re-emphasize a point of such outstanding importance, e.g. regarding anaesthetic mortality, that this message warrants repetition.

APPARATUS

This section contains manuscripts describing or evaluating the performance of anaesthetic, electromedical or related equipment.

COMMENTARY

This section of the Journal contains material which is neither a full review article nor an original article.

Appropriate material in this section would include for example, a particularly useful account of audit, the promotion of a hypothesis for subsequent experimental testing, etc.

CORRESPONDENCE

The majority of correspondence refers to articles published previously in the Journal. However, because of its rapid publication schedules, this section also allows the reader to give early notification of apparatus hazards, allergic drug reactions, etc. Correspondence should aim to be lively and topical, but controversial issues are also welcome. The Journal would like to encourage the reader to consider this avenue of publication more frequently.

BOOK REVIEWS

These are always invited by the Editor and unsolicited book reviews are never published.

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

Abstracts of the Anaesthetic Research Society have to be approved both by the Society and the Editor before being published in the Journal. Abstracts are not acceptable for publication by the Editor if abstracts of the same work have appeared in any other anaesthetic journal in the world. However, publication of an abstract does not preclude consideration of a full manuscript.

SUBMISSION OF MANUSCRIPTS

It should be noted that papers must be submitted to the Journal in accordance with the Uniform Requirements for Manuscripts for Biomedical Journals (*British Medical Journal* 1988; **296**: 401–405). A synopsis of Guide to Contributors is published in every issue of *British Journal of Anaesthesia* and authors must adhere to this. Authors who are unfamiliar with preparation of material for publication in journals should consult the Extended Guide to Contributors which was published in *British Journal of Anaesthesia* 1990; **64**: 129–136 and also appears on page 4–9 in this book.

Papers for publication and all editorial correspondence should be addressed to the Editor:

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Guide to Contributors to *British Journal of Anaesthesia*

This is a slightly modified version of the Extended Guide to Contributors that appeared in British Journal of Anaesthesia *1990; 64: 129–136.*

AIMS OF THE JOURNAL

The purpose of *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. In addition, the Journal publishes review articles and reports of new equipment.

SOME REASONS FOR DIFFICULTY

There are three principal reasons for rejection of papers:
(1) *Bad presentation.* This results from inexperience in writing scientific or clinical reports. Various manifestations of the problem may be combined in one manuscript. These include:

(a) Failure to conform to the accepted layout of a scientific paper (see below).

(b) Failure to distinguish between jargon and technical terminology (see appendix).

(c) Excessive verbosity. Most manuscripts may be shortened by at least 30% with advantage.

(d) Unsatisfactory or confusing presentation of data in tables or figures (see pages 7, 8).

(2) *Poor English style and syntax.* Although journals are not likely to be sympathetic when papers are from the English-speaking countries, *British Journal of Anaesthesia* has a long tradition of helping authors from other countries. Inevitably, however, the provision of this help causes delay.

(3) *Poor experimental design or inadequate investigation* (or both). Detailed guidance on this aspect is beyond the scope of this guide.

GUIDANCE FOR THE EARLY STAGES

Before beginning to write, analyse your objectives carefully.

What question have you tried to answer?

What message do you wish to convey?

Do the data and your interpretation of them justify the message?

It is recommended that guidance is obtained from colleagues experienced in research and in writing scientific manuscripts.

Statistical analysis is usually essential in the assessment of the validity and implications of any results presented in a paper. Statistical advice should be sought before, rather than after, the data have been collected. Do not use "recipes" for statistical analysis that you do not understand. Do not use the methods of the professional statistician unless you have a reasonable understanding of what they mean.

Do not assume that *figures* that have been prepared for photographic slides will be suitable for publication in a journal; the dimensions of a lantern slide are nearly always unsuitable for the printed page (see below).

Consult recent issues of *British Journal of Anaesthesia* and try to find a paper that conforms, in general format, to the type of preparation that you intend.

Please make sure that the *legal considerations* noted in the formal Guide to Contributors have been fulfilled. It is important to remember also that the internationally agreed code on the ethics of human experimentation (Helsinki Declaration) should be adhered to. A breach of this code will result in automatic rejection by all reputable journals. It is essential to state, where appropriate, that local Institutional Ethics Committee approval and informed patient consent have been obtained. When studies have been conducted in animals, it is essential to indicate the appropriate Home Office Licence number in the United Kingdom or note that approval has been granted by local Animal Research Committees in other countries.

SUBMISSION OF MANUSCRIPTS

British Journal of Anaesthesia participates in a uniform requirement agreement on submission of manuscripts (International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to Biomedical Journals. *British Medical Journal* 1988; **296**: 401–405).

Manuscripts must be accompanied by a covering letter. This should include: (a) Information on prior or duplicate publication or submission elsewhere of *any part* of the work. Please note that it is unethical to submit the same complete work to two journals simultaneously; a clear rejection by an editor is required before submission to a second journal should be considered; (b) a statement of financial or other relationships that might lead to conflict of interest; (c) a statement that the manuscript has been read and approved by all authors; (d) the name, address, and telephone number of the corresponding author who is responsible for communication with the other authors about revisions and final proofs.

Three copies of each manuscript (whether original or revised scripts) should be submitted to the editor. The *entire* manuscript should be presented as *double-spaced typing*; in the case of contributions from non-English-speaking countries, wider spacing is desirable. Ensure a *wide margin* (at least 7 cm). *Retain one additional copy in case of loss.*

The typical layout of the manuscript is:

Title page
Summary, including Key Words
Introduction (the heading "introduction" is not used)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Legends to illustrations

The pages should be numbered in the top right-hand corner, the title page being page *one*, etc.

Each of the three manuscripts submitted must be accompanied by a complete set of figures. One set of figures should be original, unmounted glossy prints (see below); the other sets may be photocopies.

TITLE PAGE

A separate page that includes the *title* of the paper. Titles should provide a reasonable indication of the contents of the paper. Avoid enigmatic or vague titles such as "A new method of scavenging". Titles in the form of a question, such as "Is halothane teratogenic?", are often acceptable.

The title page should include the name(s), address(es) and qualifications of author(s). It should be made clear which address refers to which author. An author's present address, differing from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols (*, †, ‡, §, ||, ¶). If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

A short running title containing not more than 50 characters (including spaces) should be included.

SUMMARY

This should appear on the second sheet and should be presented as *one paragraph* in 50–150 words. In many respects the summary is the most important part of the paper because it must convey to the reader the broad objectives of the enquiry, the principal findings and the essential conclusions. Although the reasons for the investigation may be stated, it is not necessary to give an extensive review of the precedents. Give the methods of study, in outline only, together with the principal positive findings and any important negative findings. Numerical data and probability values should be presented sparingly. List the main conclusions, but the implications of the conclusions and the more complex issues of the discussion should not be included. Statements such as "the significance of these results is discussed" are unhelpful. Only in exceptional circumstances is it appropriate to cite references. Abbreviations, other than the standard abbreviations (see below), should appear in the summary only *after* the term has been defined, and only if the term is to be repeated in the summary. In such circumstances, the term should be given once again in full in the text, with the abbreviation (in parentheses) following.

KEY WORDS

Three to five key words should be included on the summary page under the heading KEY WORDS. The system used by the Journal follows closely that devised by Greene (see *Key Words in Anesthesiology*, ed. Greene NM, 3rd Edn. Amsterdam: Elsevier, 1988).

INTRODUCTION

The introduction should give a *concise* account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has direct bearing on the present problem. For example, a description and evaluation of a system for scavenging anaesthetic gases from an operating theatre need not include an account of the previous literature of the problems of operating theatre contamination by anaesthetic gases and the many studies of morbidity, etc. which may or may not be associated with such contamination. As a rule, the introduction to a paper should not require more than about 200 words.

If a preliminary account of the results has been given in a published abstract, it is customary to refer to this.

METHODS

The title of this section may be "methods", "materials and methods" or "patients and methods". Under no circumstances should the terms "patients" and "materials" be regarded as interchangeable. While brevity is essential, the methods must be described in sufficient detail to allow the experiment to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be recounted in detail, but appropriate reference to the original should be cited. Sometimes detailed laboratory techniques may be filed separately in a recognized library and a note to this effect given in the manuscript. Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Radiometer PHM 7). When a manufacturer is unlikely to be known to readers of the Journal, the address should be provided also. In the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

Drugs. When a drug is first mentioned, it should be given by the generic or official name followed by the chemical formula in parentheses, only if the structure is not well known, and (if relevant) by the proprietary name (with an initial capital letter). A figure giving the molecular configuration of the drug is necessary only for the earliest reports of a new drug. Authors should indicate in an accompanying note to the editor the source from which they have obtained the molecular configuration; it is an important requirement that authors should check the accuracy of the configuration in every detail. Drug dosages are normally given by the name of the drug followed by the dose (e.g. diazepam 0.1 mg kg^{-1}).

Where the programme of research is complex such as might occur in a cardiovascular study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation.

Patients. Data on the age (or age range), weight, sex, height, criteria for selection, etc. should be presented, with an indication of the general state of health and type of operation being undertaken. Although it is usually possible to make such a statement in a short paragraph, a more complex presentation of information may be preferable as a table. At all times, however, it should be remembered that tables and figures are expensive to produce and should not be incorporated unnecessarily. Where it has been necessary to seek permission from the patients for the type of study being undertaken, this should be indicated.

Anaesthesia. Descriptions of methods of anaesthesia are often unnecessarily cumbersome. The following model is presented as an example of economy of words:

> The patients were premedicated with either morphine 10 mg and atropine 0.6 mg (group A) or diazepam 10 mg (group B), both given 1 h before operation. Anaesthesia was induced with thiopentone [give rate of injection where appropriate], in a dose sufficient to abolish the eyelash reflex. Suxamethonium 80 mg was given to facilitate orotracheal intubation with a cuffed tube. Anaesthesia was maintained with 0.5–1.0% halothane, in 60% nitrous oxide in oxygen, the patient breathing spontaneously from a Magill system.

Statistical analysis. Statistical methods must be described with enough detail to enable knowledgeable readers with access to the original data to verify the report and results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Confidence intervals provide a more informative way to deal with a significance test than a simple *P* value.

Additional guidance on statistics may be obtained from Guidelines for Statistical Reporting in Articles for Medical Journals (Bailar JC, Mosteller F. *Annals of Internal Medicine* 1988; **108**: 266–273).

RESULTS

Description of experimental results should be concise. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. It is not usually necessary to provide all the data that were derived in a complex study, and only those values which are essential to the communication should be entered. However, results should be presented in a manner that enables readers to check the statistical inferences. If the data are so large that this is not possible, the editor must be sent a full set with the submission of the original manuscript and the readers should be informed as to where they can obtain a similar full set of results. As a rule the following general approach should be adopted:

(1) Prepare all the data in the form of tables.
(2) Decide which data are to be presented in the communication.
(3) Can the essential data be presented succinctly in the text? If not, then essential tables or simplified tables should be prepared.

Tables are important communications and should be accompanied by a legend that makes the table self-explanatory. However, the legend must not incorporate experimental details, which should be sited more appropriately in the methods section.

Graphs and histograms based on the results should be considered only in the following circumstances:

(1) where a figure will present the data more clearly than is possible in a table,
(2) when an important trend or comparison has to be made and for which a graphic presentation is clearly superior to a table or text.

For more detailed guidance on the format of presentation of results, the reader is referred to previous issues of the Journal. A common example, however, occurs in the case of a comparison of the findings in two groups of patients who have been treated with different drug regimens. The following example is based on a manuscript submitted, with the permission of the authors:

> *First draft*
> There were 43 patients in the pethidine group and 41 in the morphine group. Table II shows that the two drug groups were evenly matched in terms of age, weight and duration of operation.
>
> Sixty to ninety minutes after the injection, there was a reduction of anxiety score of 2.9 points in the pethidine group (highly significant $P < 0.001$) and a reduction of 1.3 points in the morphine group (significant $P < 0.01$). The difference in the magnitude of the reduction of anxiety between the two groups was not statistically significant. Both groups showed a further significant reduction to normal in the anxiety rating when tested again 24 hours after the operation.
>
> Twenty-four hours post-operatively each patient was asked if she recalled seeing any picture cards before the operation. Only 12 out of 43 pethidine patients (28 %) could remember all three pictures, while 27 out of 40 morphine patients (68 %) were able to recall all three picture cards (Table III). This indicates a significantly greater incidence of amnesia with pethidine than with morphine ($P < 0.01$) using this test. This persisted for 24 hours in three pethidine and five morphine patients.
>
> Local erythema was present in twelve pethidine patients and in ten morphine patients ninety minutes after injection. This disappeared in the pethidine patients but was still present in the ten morphine patients twenty-four hours after surgery ($P < 0.01$).
>
> *Second version*
> Forty-three patients received pethidine and 41 received morphine. The groups were similar in respect of age, weight and duration of operation (table II). Sixty to 90 min after injection there was a mean reduction of anxiety score of 2.9 after pethidine ($P < 0.001$) and 1.3 after morphine ($P < 0.01$). The difference between the two groups was not significant. Both groups showed a further significant reduction to the normal range when tested 24 h after the operation.
>
> Twenty-four hours after operation each patient was asked if she recalled seeing any picture cards before operation. Only 12 of 43 in the pethidine group (28 %) could recall all three pictures, compared with 27 of 40 in the morphine group (68 %) ($P < 0.01$) (table III). This persisted for 24 h in three patients in the pethidine group and five in the morphine group. Ninety minutes after injection, local erythema was present in 12 of the pethidine group and 10 of the morphine group. This was still present 24 h after surgery only in the 10 who had received morphine.

In the results section there should be no attempt at a discussion of the findings.

DISCUSSION

This requires discipline by the writers for two reasons: first, they may feel that the task is nearly completed and that they are subject to fewer constraints; second, authors tend to read into their data more than is actually there. The form of a discussion should normally follow these headings:

(1) Summary of the major findings.
(2) Remarks qualifying in relation to these findings; for example, mention any important uncertainties in the methods of measurement.
(3) Succinct comparison of the present data and relevant data from previous studies.
(4) Deductions—which may explain important differences between the data of the present study and the data of previous studies.
(5) Conclusions from the present study. The original contribution to knowledge from the present study is stated.
(6) The implications of the conclusions for anaesthetic practice and the indications for further enquiry in this area of interest.

Authors should remember at all times, but especially in writing the discussion, that excessive length will spoil their manuscript. A discussion larger than three typed sheets should alert writers to the possibility that they have departed from the rules.

ACKNOWLEDGEMENTS

It is inappropriate to acknowledge routine assistance from nursing or surgical colleagues without which any form of clinical research would not be possible. It is essential to acknowledge all sources of financial assistance.

REFERENCES

Except for review articles, long lists of references are usually inappropriate. Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically in the reference list and numbered accordingly in both list and text.

References in text, tables and legends should be identified by arabic numbers appearing in the text in square brackets (not superscript).

Use the style of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. The titles of journals must be given in full.

Papers which carry a different system of reference will be returned to the author for retyping. The scope for major printer's errors in attempting to rectify inappropriate schemes is considerable.

References in the text. If it is considered essential to cite names of the authors of a study in the text (in addition to the identifying number), up to three names should be cited (A; B and C; D, E and F). In the case of four or more authors, "G and colleagues", "G and co-workers", "G and others" are acceptable. The expression "et al." is *never* used.

An informal reference to previous work (Z's study or Y's study) is permissible only in a paragraph that contains the reference cited formally.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Personal communications should be cited in the text as: [Brown AB, personal communication]. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned.

Papers which have been submitted *and accepted* for publication should be included in the list, the phrase "in press" replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction.

Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

There should be a *table of references* at the conclusion of the paper, starting on a new sheet. It should be prepared as follows. The names and initials of *all* authors and/or editors should be listed. The expression "et al." is *never* used.

Journals (list *all* authors). Names and initials of *all* authors, title of paper, title of journal in full, year of publication, volume number, first and last page numbers:

Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics. *British Journal of Anaesthesia* 1987; 59: 14–23.

Monographs. Name of author and initials, title of book (underlined), number of edition, town of origin, publisher, year of publication, first and last page numbers (if relevant):

Moore DC. *Regional Block*, 4th edn. Springfield, Illinois: Charles C Thomas, 1979.

Chapter in a book. The reference for an article forming part of a book should take the form:

Hull CJ. Opioid infusions for the management of post-operative pain. In: Smith G, Covino BG, eds. *Acute Pain.* London: Butterworths, 1985; 155–179.

It is a serious error to include in the list of references items which are not accurate. It is essential, therefore, that authors check the accuracy of all listed references. It is important also to check that the references listed do indeed appear in the text and *vice versa.*

PREPARATION OF TABLES

All tables should be on separate sheets and accompanied by legends that should be informative but brief and not contain information that is more appropriate to Methods. The tables should be numbered consecutively with Roman numerals. Units in which results are expressed should be given in parentheses at the top of each column and not repeated in each line of the table. Ditto signs are not used. Avoid overcrowding of tables and the excessive use of words. The format of tables should be in keeping with that normally used by the Journal; in particular, vertical lines should not be drawn. Please be certain that the data given in tables are correct, as changes at the proof stage are particularly expensive.

ILLUSTRATIONS AND FIGURES

Photographs should be unmounted glossy prints and should be protected adequately for mailing. Surfaces should not be marred by clips, pins or heavy writing on the back of the photograph.

Drawings, charts and graphs should be in black India ink on white paper and, if in sets, should be presented at uniform magnification. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text and using Arabic numerals. Each figure should be accompanied by a suitable legend.

Lettering should be professional-looking, uniform and in a common type face (preferably Univers or Helvetica). The type size of the lettering, which should be in proportion to the illustrated material, should be such that

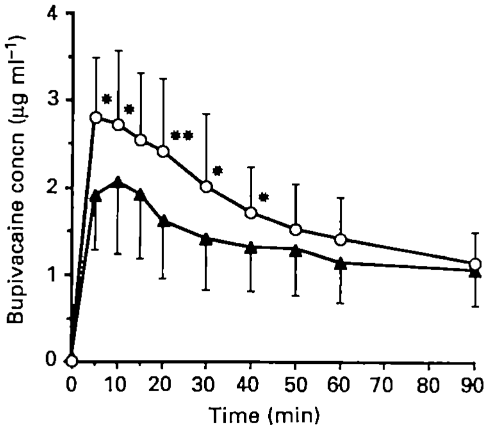

FIG. 1. Arterial plasma concentrations of bupivacaine after extradural injection of 0.75% bupivacaine plain 25 ml in 15 patients receiving low-dose adrenaline (▲) and 15 patients receiving phenylephrine (○) i.v. infusions. Mean (SD). $^*P < 0.05$; $^{**}P < 0.01$.

it will reduce to about 8-point, the size of type of figure legends in the *British Journal of Anaesthesia* (see example). For publication, illustrations are reduced to single column width (or for particularly complex diagrams, to widths between single and double column).

It should be borne in mind that reduction of figures results in an accompanying reduction in boldness (thickness) of all parts of the figure. It is thus inappropriate to use a variety of boldness of axes, graph lines and lettering in one figure, or to present a figure drawn to a large scale in fine lines and with small, fine lettering. The typewriter line thickness of computer printouts to A4 size is thus to be avoided. The problem of computer-produced diagrams may be obviated by programming the computer to produce a diagram of the same size as that of the final published diagram or, alternatively, to produce lines and lettering of large thickness so that photoreduction results in the appropriate size.

Care should be taken that the labelling of axes does not extend the dimensions of the figure substantially. Avoid suppression of the zero point (the axes may be broken (/ /) if required). (*See also* Units, symbols and abbreviations below.)

The foregoing advice, which may not be completely intelligible to many authors, will be understood by a professional illustrator whose advice should be sought in most circumstances. It should be emphasized that the dimensions of a figure prepared for a photographic slide are often unsuitable for reproduction on the printed page. Symbols that are to appear in the legend should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇◑ × +

Magnifications, especially in photomicrographs should be indicated on the photograph itself by an unlabelled scale bar that would remain appropriate after reduction. Indicate in the legend the length of the bar.

Accuracy in the preparation of figures is essential as is the appropriate use of symbols and abbreviations (see below), as alteration to figures or the re-drawing of them by the publisher is an expensive matter and the cost may have to be borne by the author.

Never dispatch figures or photographs unless a suitable version has been retained on file that may be copied easily in the event of loss.

UNITS, SYMBOLS AND ABBREVIATIONS

British Journal of Anaesthesia, in common with other journals in the United Kingdom and many other countries, uses the S.I. system of units with a few notable exceptions (pH and intravascular and ventilatory pressure measurements, which should be given in the units of calibration, e.g. mm Hg, cm H_2O). Blood-gas tensions and the partial pressures in the gas phase should be given in the appropriate S.I. unit (kPa for kilopascal). It is not intended to give a detailed account of the S.I. system, the notation of units, symbols and abbreviations in this document. Readers are referred to *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors*, 4th Edn. Baron DN, ed. (1988), published by and available from the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE.

Particular problems have arisen in relation to the *notation* of units which was introduced at the same time as the change to the S.I. system. Avoid the use of the solidus (/) in favour of various units of the expression set on one line. In the case of expressions "below the line" superscript $^{-1}$, $^{-2}$, etc. as appropriate is given. Thus for drug dosage we write:

$$\mathrm{mg\ kg^{-1}}$$

A Guide for Biological and Medical Editors and Authors (Baron, 1988) lists also the abbreviations which may be used by authors without previous definition of their meaning. As noted above, all other abbreviations must be defined, once in the summary and once in the text.

In addition, the "Pappenheimer" system of abbreviations of respiratory terms is acceptable without definition (Pappenheimer JR, Comroe JH, Cournand A, Ferguson JKW, Filley GF, Fowler WS, Gray JS, Helmholtz HF, Otis AB, Rahn H, Riley RL. Standardisation of definitions and symbols in respiratory physiology. *Federation Proceedings* 1950; **9**: 602–605).

FURTHER READING FOR AUTHORS

While it is hoped that this extended guide to contributors will be of value to those writing for *British Journal of Anaesthesia*, it should not be regarded as comprehensive instruction for those preparing manuscripts. Several simple texts and papers have been prepared on this subject and it is essential that the author preparing his first manuscript should avail himself of these. We commend particularly Professor Hugh Dudley's book entitled *The Presentation of Original Work in Medicine and Biology*, published by Churchill Livingstone in 1977. In addition, we recommend that authors should be familiar with Eric Partridge's *Usage and Abusage—A Guide to Good English*, published by Hamish Hamilton in several editions. Sir Ernest Gowers' *The Complete Plain Words*, revised by Whitcut and Greenbaum, is published by Penguin Books and is a source of common sense in writing. In the matter of spelling, *British Journal of Anaesthesia* follows the *Shorter Oxford English Dictionary*.

APPENDIX

(This list is representative of the errors and unacceptable usage which occur commonly.)

Administered—prefer given for simple injection of drugs.

Astrup—this is not a collective term for methods of blood-gas measurement.

Blood-gases—specify carbon dioxide, $P\mathrm{CO}_2$, etc.

Blood pressure—avoid this term in favour of arterial pressure, etc. Specify mean, systolic, diastolic.

Case—this should not be regarded as interchangeable with the term "patient". An account of the management of a patient may be referred to as a "case history" or "case report".

Chronic bronchitics—avoid this expression when you mean patients with chronic bronchitis.

Compared—compared *with* is usually preferable in scientific writing. Compared *to* means liken to and may be used correctly by poets.

Data—plural.

Due to—avoid unless in the description of a financial debt. *Because of* and *as a result of* are preferable.

Employed—prefer *used*.

Fall and *Rise*—avoid these expressions which suggest a gravitational influence. *Decrease* or *reduction* and *increase* are preferable.

Following—prefer *after*.

Groups—avoid expressions such as "thiopentone patients" and "cholecystectomy patients" in favour of "patients receiving thiopentone" and "patients undergoing cholecystectomy". It is permissible, however, to refer to the "thiopentone group" or "cholecystectomy group".

High and low—avoid if you mean large and small.

Incidence—this refers to the proportion of a defined group developing a condition within a stated period. *Frequency* is the number of subjects (expressed usually as a percentage) with a condition. *Prevalence* is frequency at a particular time.

Length (of time)—prefer *duration*.

Level—avoid in favour of *concentration*.

Multiple adjectives—avoid using an adjective in apposition to a noun, e.g. "concentration of sodium" is preferable to "sodium concentration".

Numbers—should be spelled out if less than ten, and always at the start of a sentence.

Postoperatively and *preoperatively*—prefer *after operation* or *before operation*.

Postoperative (*preoperative*) *treatment*—acceptable.

Prior to—prefer *before*.

Protocol—this word has connotations which are chiefly concerned with diplomacy. The word should not be used to describe a scheme of study in an experiment. The term *programme* is to be preferred.

Regime—is a political institution. Prefer *prescription, scheme, regimen* or *infusion*, as appropriate.
Relaxants—avoid in favour of "myoneural blocking drugs", "myoneural blocker", "neuromuscular blocker".
Rotameter—note capital letter.
Scopolamine (and *Omnopon*)—use approved names, *hyoscine* and *papaveretum*
Sexist pronouns—avoid using *he* and *him* to refer to both sexes; prefer *they*.
Showed—prefer *was present* or *occurred*.
Significant—avoid expressions such as "highly significant" or "very highly significant", in favour of *significant* with a probability value in brackets.
Sleep-dose—this is vague. Prefer *a dose sufficient to obtund the eyelash reflex*, etc.
Stable (of measurements)—prefer *unchanged*.
Suxamethonium—not succinylcholine or Scoline.
Teflon—note capital letter.
Tendency to change—changed.
Utilize—prefer *use* unless referring to resources or substrates.

It is important to avoid conversational expressions such as:
"the patient was ventilated" (the lungs were ventilated)
"the patient was intubated" (the trachea was intubated)
"the patient was placed on a ventilator" (ventilation was controlled artificially)
"the patient was taken off the ventilator" or "the patient was weaned from the ventilator" (artificial ventilation was discontinued)
"the patient was extubated" (the tracheal tube was removed).

National and International Bodies in Anaesthesia

ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN AND IRELAND

The Association of Anaesthetists of Great Britain and Ireland was founded in 1932 and in 1992 celebrated its Diamond Jubilee. The purpose of the Association is to promote the development and study of anaesthesia and its recognition as a specialized branch of medicine. It represents some 2200 ordinary members in Great Britain and Ireland, 2100 members in training and 750 members overseas. The official journal of the Association is *Anaesthesia* and it publishes a monthly newsletter, *Anaesthesia News*.

The affairs of the Association are governed by its Council which comprises the President, Past President, Vice-Presidents, Honorary Treasurer, Honorary Secretary, Assistant Honorary Secretary, Assistant Honorary Treasurer and the Editor of *Anaesthesia*, together with 12 elected members. In addition, the following co-opted members currently sit on Council—the President of the Royal College of Anaesthetists, the Dean of the Faculty of Anaesthetists, Royal College of Surgeons in Ireland, the Editor of *Anaesthesia News*, a representative of Her Majesty's Forces, the Convenor, Irish Standing Committee, and the Honorary Secretary of the World Federation of Societies of Anaesthesiologists. The Committee of the Group of Anaesthetists in Training represents members of the Association who are trainees, and its Chairman and Secretary are *ex officio* members of Council. Council is supported by the Advisory Committee, the Editorial Board, the Finance Committee, the Education and Research Committee, the Safety Committee, the Committee of the Group of Anaesthetists in Training, the International Relations Committee and the Private Practice Committee.

Working Parties are constituted to study specific problems and at present topics under discussion include Assistance for Anaesthetists, Services for Chronic Pain, Departmental Accommodation and Secretarial Assistance, Work Load for Non-consultant Grades, Limited Life Equipment and HIV and other blood borne viruses. The Association is represented on the Anaesthetics Sub-Committee of the CCSC, the Joint Committee for Higher Training of Anaesthetists, the National Confidential Enquiry into Perioperative Deaths, the British Standards Institute and the Mono-Specialist Sub-Committee of the UEMS.

The Association organizes an Annual Scientific Meeting in conjunction with the Annual General Meeting, an Annual Winter Scientific Meeting, an Annual Meeting for anaesthetists in training and, in conjunction with the Royal College of Anaesthetists, a Continuing Medical Education Day. In addition, the Association runs an extensive seminar programme on a wide range of topics.

The Association awards a Research Fellowship (up to two years), a Travelling Fellowship sponsored by Baxter Health Care Limited, and grants for research, travel and other educational purposes. Jointly with the Royal College of Anaesthetists, the Association sponsors a Senior Lecturer post in Intensive Care. Each year, the Association awards a prize(s) for original papers presented at the Annual Prize Competition at the Annual Meeting of the Group of Anaesthetists in Training. In addition, an Undergraduate Essay Prize(s) is awarded annually.

Communications to the Association should be addressed to Dr R. S. Vaughan, Hon. Secretary, Association of Anaesthetists of Great Britain and Ireland, 9 Bedford Square, London WC1B 3RA. Tel. 071-631 1650; Fax 071-631 4352.

Communications to *Anaesthesia* should be addressed to Dr M. Morgan, The Editor, *Anaesthesia*, Department of Anaesthetics, Hammersmith Hospital, Du Cane Road, London W12 0HS. Communications to *Anaesthesia News* should be addressed to Dr J. E. Charlton, The Editor, *Anaesthesia News*, 5 Woodbine Avenue, Gosforth, Newcastle-upon-Tyne NE3 4EU.

Current Officers:

President: Dr W. R. MacRae (Edinburgh)
Vice-Presidents: Dr Margaret L. Heath (Lewisham)
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Editor: Dr M. Morgan (London)

ASSOCIATION OF PROFESSORS OF ANAESTHESIA

The Association of Professors of Anaesthesia meets once each year to discuss all matters of importance to the specialty, but particularly those concerning teaching, training and research. In addition, the Association meets annually with the President of the Royal College of Anaesthetists to discuss subjects of shared interest. The Association belongs to the Federation of Associations of Clinical Professors and has two members on the Joint Committee for Higher Training of Anaesthetists.

Current Officers:

Chairman: Professor A. R. Aitkenhead, University Department of Anaesthesia, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH. Tel. 0602-709229 (direct line); Fax 0602-700739.

Secretary: Professor C. S. Reilly, University Department of Anaesthesia, Medical School, Beech Hill Road, Sheffield S10 2RX. Tel. 0742-700295; Fax 0742-728622.

EUROPEAN ACADEMY OF ANAESTHESIOLOGY

The European Academy of Anaesthesiology, founded in September 1978, is composed of 500 individual members who aim to raise the standard of practice, teaching and research in anaesthesiology throughout the European sphere. Membership is by election and open to any specialist practitioner in good standing. Affiliate membership is open to those who pass the Academy examination (the European Diploma in Anaesthesiology and Intensive Care) and to Anaesthesiologists outside Europe.

The European Diploma is a two-part examination; Part 1, in September of each year, consists of MCQs and is available in five languages. This can also be set as an in-training examination by trainees in Academy-registered centres. Part 2 consists of vivas and is also multi-lingual.

The Academy publishes the *European Journal of Anaesthesiology* (editor Professor M. D. Vickers, Tel. 0222-743110).

For details concerning the examination write to: The Examination Secretary, 9 Bedford Square, London WC1B 3RA. Tel. 071-631 1650/4352.

For journal subscriptions contact: Blackwell Scientific Publications Ltd., Osney Mead, Oxford OX2 0EL.

Membership details may be obtained from: Professor J. C. Otteni, Service d'Anésthesie-Réanimation, Hôpital de Hautepierre, Avenue Molière, F-67200 Strasbourg Cedex, France. Tel. 010 33 88289000; Fax 010 33 88285464.

EUROPEAN ASSOCIATION OF CARDIOTHORACIC ANAESTHESIOLOGISTS (EACTA)

The Association was conceived on 10 May 1985 during a symposium on cardiac anaesthesia in Leiden attended by an international group of anaesthetists.

Dr Ray Latimer organized the inaugural meeting which took place in Cambridge on 17–18 June 1986. It was at this meeting that the constitution was presented and EACTA was officially born. The Association has now a membership of 315.

The seventh Annual Scientific Meeting (1992) took place in Maastricht, The Netherlands; the eighth (1993) will be in Zurich, Switzerland; and the ninth (1994) in Turku, Finland.

The aim of EACTA is to be a forum in Europe for international scientific discussions and exchange of ideas in the field of cardiothoracic anaesthesia and related topics, and to promote education and development in this field.

The activities of the Association include: an Annual Scientific Meeting on Cardiothoracic Anaesthesia in Europe; the award of prizes to encourage a high standard of scientific presentation; the award of scholarships to assist in funding scientific investigation and enable educational visits to centres in other countries; and the publication of abstracts of papers presented at the scientific meetings in the *Journal of Cardiothoracic and Vascular Anaesthesia*.

The governing body of the Association is the Representative Council which is comprised of one member from each country in both East and West Europe. At present, there are 25 countries represented.

Membership is open to all interested in the field of cardiothoracic anaesthesia. The official language is English.

Further information can be obtained from: Hon. Secretary—EACTA, Dr Ray Latimer, Department of Anaesthesia, Papworth Hospital, Papworth Everard, Cambridge CB3 8RE. Tel. 0480-830541 (ext. 406); Fax 0480-831146.

Current Officers:

Chairman:	Hans Sonntag (Göttingen)
Deputy Chairman:	Olav Sellevold (Trondheim)
Secretary and Treasurer:	Dr R. Latimer (Cambridge)
Scientific Secretary:	Hans Tydén (Uppsala)
Membership Secretary:	Jean Neidecker (Lyon)
Organizer 1992 and past Chairman:	Simon de Lange (Maastricht)
Organizer 1993:	Edith R. Schmid (Zurich)
Organizer 1994:	Jouko Jalonen (Turku)

EUROPEAN SOCIETY OF REGIONAL ANAESTHESIA

The European Society of Regional Anaesthesia (ESRA) was founded in January 1980 as an International Scientific Association (Belgian Bulletin of Acts, Orders and Decrees, 15 May 1980).

The functions of the ESRA include: promoting research in loco-regional anaesthesia and its publication in existing scientific journals; organizing an Annual European Congress, as well as national and regional meetings and workshops. Languages used are the languages of the zone in question and English (for the Annual Congress English is used).

The Society divides Europe into seven zones, each of which has a Zone Representative. Great Britain and Ireland constitute Zone 2 whose representative is Dr A. Rubin.

The first Annual Meeting of the ESRA was held in Edinburgh in 1982 and international meetings are held in major European centres annually. In addition, a Great Britain and Ireland Annual Scientific Meeting is held, usually in March.

The Society shares the journal *Regional Anesthesia* with the American Society of Regional Anaesthesia.

For further information contact: Dr John H. McClure, Membership Secretary/Treasurer of the Great Britain and Ireland Sub-Committee, Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW. Tel. 031-229 2477; Fax 031-229 3337.

Current Officers:

President:	Dr Albert Van Steenberge
Hon. Secretary:	Dr Andre Van Zundert

FACULTY OF ANAESTHETISTS OF THE ROYAL COLLEGE OF SURGEONS IN IRELAND

The Faculty of Anaesthetists, founded in 1959, is located in the Royal College of Surgeons, St Stephen's Green, Dublin 2.

The Faculty undertakes the Parts 1 and 2 and Final Examinations for the Diploma of Fellowship of the Faculty of Anaesthetists (F.F.A.R.C.S.I.). In addition, Parts 1 and 2 and the Final Fellowship courses are co-ordinated by the Faculty before the relevant examinations. The Faculty provides exchange examiners for the Royal College of Anaesthetisits examination and external examiners, upon request, for overseas Fellowship and university examinations.

Higher Professional Training in the Republic of Ireland is co-ordinated by the Medical Advisory Committee of the Faculty. This body also advises statutory bodies in the Republic of Ireland on anaesthetic related issues. The Faculty, along with the Royal College of Anaesthetists, Scottish Standing Committee of that College, the Association of Anaesthetists of Great Britain and Ireland and the Association of University Professors of Anaesthesia, comprise the Joint Committee for Higher Training of Anaesthetists.

Five-yearly inspections are undertaken of hospitals accredited by the Faculty for General Professional Training in the Republic of Ireland. The Faculty provides a comprehensive continuing medical education programme, including a two-day Annual Scientific Meeting; a cojoint meeting with the Intensive Care Society in March, and a Registrars' Research Meeting. The proceedings of the Faculty are published in the quarterly *Journal of Irish Colleges of Physicians and Surgeons*. In addition, an annual faculty newsletter is published in May.

The activities of the Faculty are co-ordinated by the Board of Faculty. Faculty Board subcommittees include examination, education, finances and general purposes, medical advisory, quality assurance and hospital inspection. The Board of the Faculty of The Royal College of Surgeons in Ireland 1992/1993 comprises:
Professor R. S. J. Clarke (*Dean*)
Dr Michael Slazenger (*Vice-Dean*)
Professor A. J. Cunningham (*Honorary Secretary*)
Dr John Cooper (*Honorary Treasurer*)
Dr W. Blunnie
Dr J. P. H. Fee
Dr P. Fitzgerald
Dr J. Gardiner
Dr A. M. Hainsworth (*Chairman Education Committee*)
Dr S. M. Hart (*Chairman Examination Committee*)
Dr D. Hogan
Dr N. T. Kenny
Dr S. Kielty
Dr M. MacEvilly
Dr R. MacSullivan (*Chairman Medical Advisory Committee*)
Dr W. McCaughey
Dr C. McDowell
Dr D. Phelan
Dr A. Sharkey

Further information may be obtained from: Professor Anthony J. Cunningham, Honorary Secretary, The Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin 2. Tel. Dublin 780200 (ext. 2234); Fax Dublin 780018.

JOINT COMMITTEE FOR HIGHER TRAINING OF ANAESTHETISTS

The Joint Committee for Higher Training of Anaesthetists, founded in 1970, consists of representatives of the Royal College of Anaesthetists, the Scottish Standing Committee of that College, the Faculty of Anaesthetists of the Royal College of Surgeons in Ireland, the Association of Anaesthetists of Great Britain and Ireland, and the Association of University Professors of Anaesthesia.

It is understood that Higher Training in Anaesthesia should be a logical continuation of the Basic Specialist Training which leads to the acquisition of the diploma of F.R.C.Anaes. or F.F.A.R.C.S. Ire. In addition to providing experience and training in those aspects of anaesthesia to which the trainee did not have adequate exposure during pre-Fellowship training, the Higher Training period should give the prospective consultant progressively increasing responsibility and the ability to undertake, under consultant supervision, all the duties that he or she will eventually discharge independently. The objective is to ensure that trainees are given the opportunity to gain experience, both in breadth and in depth, in a wide range of anaesthetic methods and types of surgery.

Trainees are expected to attend regular clinical meetings with consultant staff and to undertake some responsibilities for the training and teaching of anaesthetists in training, auxiliary staff and, where possible, medical undergraduates. In particular, they should take part in the giving of in-service lectures and tutorials to anaesthetists in training undergoing Basic Specialist Training.

Higher Training will normally occupy a minimum of three years of which at least two years must be spent in clinical anaesthesia. A certificate of accreditation will not be granted to any trainee who has not acquired a minimum of five years' experience in the speciality of anaesthesia.

There is now a requirement that at least two of the three years of Higher Training must have been spent in specifically approved senior registrar posts in the United Kingdom or Republic of Ireland.

The period of Higher Training offers opportunities for research activities and the Joint Committee believes that every encouragement should be given to the trainee to take advantage of these, under appropriate guidance. In most instances it will be sufficient for the trainee to participate in some clinical investigation. However, a period of up to one year spent whole-time in a relevant university department or other approved institution in the United Kingdom, the Republic of Ireland or overseas may be accepted by the Joint Committee towards accreditation, provided that the experience has been acquired in a post either specifically recognized by the Joint Committee or in respect of which prospective approval of the proposed research has been obtained from the Joint Committee. Since the latter case is more common, the importance of obtaining *prior* approval from the Joint Committee is stressed.

A maximum of one year of training experience acquired under supervision in a centre outside the United Kingdom and the Republic of Ireland may be accepted towards accreditation. Approval of such experience must be obtained prospectively, since no centre outside the United Kingdom and the Republic of Ireland is specifically recognized for Higher Training by the Joint Committee.

Post-Fellowship anaesthetic training leading to accreditation must be acquired in specifically approved senior registrar or senior registrar equivalent posts. It is not possible for the Joint Committee to count towards accreditation post-Fellowship experience acquired in non-training posts such as staff grade, associate specialist or clinical assistant. Senior registrar equivalent experience usually takes the form of post-Fellowship registrar training in anaesthetics and may be accepted by the Joint Committee upon individual applications from the trainees concerned.

The Joint Committee will consider the submission of part-time training programmes for senior registrars, on condition that the programmes provide for a minimum contribution from part-time trainees of five clinical sessions per week plus adequate provision for emergency work.

On entry into an approved Higher Training programme, the trainee should apply for enrolment with the Joint Committee. No fee will be charged for enrolment. Eligibility for enrolment will depend on the possession of the F.R.C.Anaes. or F.F.A.R.C.S. Ire. diploma or of acceptance by the Joint Committee of evidence of completion of comparable anaesthetic training. On completion of the designated period of Higher Training, the Joint Committee will ask for a report from the appropriate consultant-in-charge of training to the effect that the period of Higher Training has been carried out satisfactorily and upon receipt of the report will recommend to the appropriate college or faculty that a Certificate of Accreditation be granted.

Accreditation will represent a clear recognition by the college or faculty of the holder's eligibility for consultant responsibility, although it cannot in itself be a guarantee of appointment to that grade, or of suitability for a particular consultant post, factors which will be determined by a health authority on the recommendation of a statutory Advisory Appointments Committee. It should be underlined also that accreditation represents the attainment of the minimum requirements for a consultant appointment, and that possession of a Certificate of Accreditation does not imply that all holders are equal, since they will demonstrate widely differing abilities and ambitions, and a variety of specialized experience.

While training programmes must provide the widest possible range of anaesthetic experience the Joint Committee recognizes the importance of flexibility and of adapting the training programmes to the individual abilities and preferences of the trainees.

Further information or advice can be obtained from the appropriate Regional Educational Adviser and Miss Christine Peddle, Administrative Secretary, Joint Committee for Higher Training of Anaesthetists, 48–49 Russell Square, London WC1B 4JY. Tel. 071-813 1900; Fax 071-813 1876.

Current Officers:

Chairman:	Professor A. A. Spence
Deputy Chairman:	Professor R. S. J. Clarke

NORTHERN IRELAND SOCIETY OF ANAESTHETISTS

The first grouping of anaesthetists for scientific purposes took place in 1941. Meetings were held originally in members' houses. In 1945 the Society was affiliated to the British Medical Association but became an independent body in 1972. The Society has now a membership of approximately 200.

Aims and objectives of the Society are the propagation of scientific knowledge concerning anaesthesia and allied subjects for both senior and junior anaesthetists in Northern Ireland. The Society is run by a committee which is composed of the President, Vice-President, Honorary Secretary and eight others including a junior member. The Committee holds office for two years.

Seven scientific meetings are held each year between October and April. These are usually held once a month on a Wednesday evening and rotate through the teaching hospitals. A Presidential Address is given on alternate years. The Society also awards a Registrars' Prize for research (Dundee Medal). The meetings have both a scientific and social format with a meal and refreshments following the speaker's address.

For further details write to Mrs N. Collins, Northern Ireland Society of Anaesthetists, c/o Department of Anaesthetics, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland. Tel. Belfast 245133 (ext. 2236).

Current Officers:

President:	Professor R. S. J. Clarke
Hon. Secretary:	Dr P. Elliott

ROYAL COLLEGE OF ANAESTHETISTS

The Royal College of Anaesthetists is the professional body whose function it is to provide, maintain and develop the standards of anaesthesia within the U.K.

The first such professional body created was the Faculty of Anaesthetists of the Royal College of Surgeons of England in 1948 which became the College of Anaesthetists in 1988. The college became the Royal College of Anaesthetists under the grant of a Royal Charter on March 16, 1992.

There are 5500 Fellows of the College 3400 of whom practice within the U.K., and also 250 annually-subscribing Members of the College. The Fellows elect a governing Council of 20 who in turn elect a President and two Vice-Presidents.

The main functions of the College can be divided into four main areas: the examination systems, the recognition of training schemes, education, and finally, the relationships with other bodies and notably, government.

Examinations. The College confers two diplomas by examination. The D.A. is gained by passing the Part 1 Fellowship examination and by practising in a recognized hospital for 12 months. The Fellowship is gained by completing at least two years in recognized training posts and by passing the Part 2 and Part 3 examinations. The Part 1 examination is concerned with the broad general principles of anaesthesia relevant to an SHO in the first year of training, Part 2 deals with the applications of the relevant basic sciences to anaesthesia and Part 3 encompasses a much broader range of experience. The College publishes a *Guide to Training* document which gives details of the examination syllabus, the appropriate regulations and other relevant matters. This is included in this Handbook (see pages 67–75). The Council of the College has decided that an additional Diploma in Intensive Therapy will shortly be offered. It will be intended principally for anaesthetists at senior registrar level who intend to take a major role in intensive care when becoming consultants.

Recognition of training schemes. Anaesthetic training in the U.K. can be divided into two main stages. Basic Specialist Training is that which leads to the Fellowship and involves time spent at SHO and registrar grades. The training is supervised and all schemes and hospitals are inspected to ensure compliance with the standards. The College publishes a *Basic Specialist Training Guide* which is included in this Handbook (see pages 76–80). Training at senior registrar levels is supervised via a Joint Committee for Higher Training of Anaesthetists which includes members from the Irish Faculty of Anaesthetists, the Association of Anaesthetists, the Association of Professors in Anaesthesia, the Department of Health and a representative of Anaesthetisits in Training. A *Higher Specialist Training Guide* is included in this Handbook (pages 81–84).

The College also is committed to the Joint Advisory Committee on Intensive Therapy, an inter-collegiate body, which supervises 2-year training programmes for a small number of anaesthetic, medical or surgical senior registrars who wish to specialize in intensive therapy.

Education. The College organizes an extensive educational programme at national level and is encouraging programmes in the regions. Nationally, there is an Anniversary Forum in March, a Scientific Meeting in May, a two-day symposium in November and a joint meeting with the Association in the autumn. Short courses for those preparing for the Parts 2 and 3 examinations are also organized. Details of all these may be obtained from the College Education Department.

Bernard Johnson Adviser. The Council appoints a Bernard Johnson Adviser in Anaesthetics whose main function is to advise trainees and, in particular, those from overseas as to suitable training posts in the U.K. Dr D. A. Saunders is the current adviser. His duties also encompass counselling for those trainees having problems with the examinations.

Relationships with other bodies. The College is represented on all appointment committees for registrar, senior registrar and consultant posts and usually advises also at appointments for university posts. The College's Regional Educational Advisers review the content of all advertised consultant and staff doctor posts to ensure they conform with the College's recommendations.

The College advises the Department of Health and the equivalent bodies in Scotland and Northern Ireland on many matters and especially on manpower requirements. An increasing activity is the development of audit and matters pertaining to quality of practice. The College has created a Quality of Practice Committee which is developing national initiatives and has some funds to encourage local initiatives which may be applicable generally.

The College has close links with the Association of Anaesthetists and there have been a number of joint publications.

The College's official journal is the *British Journal of Anaesthesia*. The College also publishes a *Newsletter* which reports matters of interest to Fellows.

Relationship with Fellows. The College has established a network of Regional Educational Advisers and Deputies for the Health Service Regions in England, and for Health Boards in Wales, Scotland and Northern Ireland. They are supported by College Tutors in each health district. The advisers and tutors are responsible for ensuring the adequacy of anaesthetic training and for the maintenance of the standards of anaesthesia set by the College. There is an annual meeting of advisers and one for tutors at which problems can be discussed and information disseminated both by and to the Council.

Finance. The College's main source of income is from the subscriptions of the Fellows. Additional funds are generated to a small extent by the other activities and by grants from the Department of Health to support the training recognition programmes and the Quality of Practice unit. The College needs substantial additional funds to develop its new headquarters in London. The Anaesthetic Academic Foundation is coordinating a national appeal to Fellows, to industry and to all who can help. Anaesthetists can help by donations, by covenants and by using Canlocum through which funds generated by independent practice can by channelled to the appeal. Further details may be obtained from the Appeal Director (Mrs Alethea Rogers) at the College.

Current Officers:

President:	Professor A. A. Spence
Vice-Presidents:	Professor D. J. Hatch Dr J. Lumley
Finance Secretary:	Mr K. Loney
Appeal Director:	Mrs A. Rogers
Bernard Johnson Adviser:	Dr D.A. Saunders

The members of Council are:

Professor A. A. Spence (Edinburgh)
Professor D. J. Hatch (London)
Dr Jean Lumley (London)
Professor M. Rosen (Cardiff)
Dr P. J. F. Baskett (Bristol)
Professor C. Prys-Roberts (Bristol)
Professor J. Norman (Southampton)
Dr F. R. Ellis (Leeds)
Professor C. J. Hull (Newcastle)
Dr Sheila Willatts (Bristol)
Dr J. C. Stoddart (Newcastle)
Dr W. R. MacRae (Edinburgh)
Dr P. Morris (Manchester)
Professor A. P. Adams (London)
Professor T. E. J. Healy (Manchester)
Dr K. Budd (Bradford)
Dr Doreen R. G. Browne (London)
Professor G. Smith (Leicester)
Dr A. P. Rubin (London)
Professor L. Strunin (London)

For further information on any of the College's activities contact: The Chief Executive, Royal College of Anaesthetists, 48–49 Russell Square, London WC1B 4JY. Tel. 071-813 1900; Fax 071-813 1876.

ROYAL SOCIETY OF MEDICINE (SECTION OF ANAESTHETICS)

In the first decade of the present century, the various medical societies in London joined to form the Royal Society of Medicine, a multi-specialist organization which is now one of the largest of its kind in the world. The Society possesses the most comprehensive library of medical books available in the United Kingdom.

The Section of Anaesthetics of the Royal Society of Medicine, which was established in 1908, grew in its influence and anaesthetists from all over the country (and later from all over the world) looked to the Section of Anaesthetics of the Royal Society of Medicine as a meeting place and as a forum for the presentation of the results of their research. Several major advances in the speciality were reported first to the Section (controlled respiration, muscle relaxants and volatile anaesthetics).

The Section of Anaesthetics' meetings are among the best attended meetings held by the Society. The officers of the Section of Anaesthetics are a President, two Secretaries, four Vice-Presidents and 20 ordinary members of Council (including anaesthetists in training). Membership of the Section of Anaesthetics now totals approximately 470.

Intending members of the Section of Anaesthetics must first be elected a Fellow of the Society, who are then entitled to join up to three Sections and to attend any of the Section meetings. The subscription varies according to seniority and place of residence, but there is no further charge for Section membership.

The Section of Anaesthetics of the Royal Society of Medicine meets usually on the first Friday of the month at 17:30 from October until June. The Section holds its annual dinner after one of the meetings in the Spring or Summer. The Section also holds one-day symposia on matters of wide interest to anaesthetists. Every year a Registrar's prize with gold medal is offered for essays by anaesthetists in training on anaesthetic subjects. Joint meetings of the Sections of the Royal Society of Medicine provide opportunities for anaesthetists to come into contact with other specialists.

As well as providing a scientific forum, the Royal Society of Medicine provides club facilities. Lunch and tea are available on the Society's premises every weekday and dinner is served in the evenings. The Society maintains club premises in the Domus Medica on the first floor where, if accommodation is available, Fellows may be accommodated at reasonable cost during stays in London.

The Society publishes a monthly journal (*Journal of the Royal Society of Medicine*) which contains some of the material presented at the meetings of the Section. The journal includes contributions related to all branches of medicine and is a fully refereed and cited journal.

Application forms for membership and diary cards can be obtained from: The Sections Officer, Section of Anaesthetics, The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Tel. 071-408 2119; Fax 071-355 3197.

Current Officers:

President:	Dr I. R. Verner
Hon. Secretaries:	Dr G. B. Rushman (Tel. 0702-586379) Dr Anne Florence (Tel. 051-728 7532)

SCOTTISH SOCIETY OF ANAESTHETISTS

The Scottish Society of Anaesthetists, founded in 1914, is the oldest National Society of Anaesthetists in the world. The aims of the Society are to further the study of the science and practice of anaesthesia and the proper teaching thereof and to conserve and advance the interests of anaesthetists. Membership is restricted to members of the medical profession practising the speciality of anaesthesia. The annual subscription is £10 and there are approximately 450 members.

The Society organizes three major meetings each year: the Annual General Meeting in April, the Registrars' Meeting usually held around June and the Annual Scientific Meeting held in November. The Scientific Meeting also includes the Gillies Memorial Lecture, a lectureship endowed in honour of Dr John Gillies. At the Annual General Meeting there is a Guest Lecturer and the Presidential Address. The Society organizes a Registrars' Paper Competition and the winner is awarded a prize of £250.

The Society publishes yearly the *Annals of the Scottish Society* which contains transcripts of the papers given at all the meetings and various other items of Society news.

For further information contact: Dr J. D. MacKenzie, Hon. Secretary, Department of Anaesthesia, Aberdeen Royal Infirmary, Aberdeen AB9 2ZB. Tel. 0224-681818 (ext. 53144); Fax 0224-685307.

Current Officers:
President: Dr J. Wilson
Hon. Secretary: Dr J. D. MacKenzie
Hon. Treasurer: Dr I. Levack

WORLD ASSOCIATION FOR EMERGENCY AND DISASTER MEDICINE

Originally formed as the Club of Mainz, the World Association for Emergency and Disaster Medicine (WAEDM) aims to synthesize original research and practical experience to improve the delivery of everyday and mass casualty and prehospital emergency medical care. Additionally, the Association is working to formulate guidelines for health planners in mass disaster preparedness and is establishing an international network of medical professionals who will be able to render competent field assistance at disaster scenes.

The WAEDM, formed in 1976, maintains working task forces on disaster planning, international disaster relief, hazardous materials and aircraft disasters, and convenes World Congresses on Emergency and Disaster Medicine every two years to further this ongoing work.

The Congresses are rotated to different locations around the globe and bring together researchers, policy makers, practitioners and teachers from the international emergency medicine community. Delegates enjoy the unique opportunity for informal interchange with those Association members who are world renowned authorities in trauma care, resuscitation, immediate prehospital care and disaster relief.

Past world congresses have been held in Mainz (Germany), Pittsburgh (USA), Rome (Italy), Brighton (UK), Rio de Janeiro (Brazil), Hong Kong and Montreal (Canada). Future congresses will be held in Stockholm (Sweden) in 1993 and in Jerusalem in 1995.

Papers presented at the Congresses and general recommendations and conclusions generated by these collaborative efforts are published in the Association's quarterly journal *Prehospital and Disaster Medicine* which is produced in conjunction with the National Association for Emergency Medical Services Physicians (NAEMSP).

Membership of the WAEDM provides an international link with others who are actively involved with emergency and disaster medicine and includes a subscription to the journal, updates on recommendations and reports from both the General Assembly and the Task Forces and the opportunity to participate in the World Congresses. Members will also receive documents concerning the organization's structure, a description of the overall goals, a Directory of Members and a membership identification card. The current membership of the Association is 500.

Further information can be obtained from: Dr Peter J. F. Baskett, Consultant Anaesthetist, Frenchay Hospital, Bristol BS16 1LE. Tel. 0272-702020; Fax 0272-574414 or from: Dr S. W. A. Gunn, Membership Secretary, 1261 Bogis-Bossey, Geneva, Switzerland. Tel. 010 41 227 793 4433.

Current Officers:
President: Dr P. J. F. Baskett
Hon. Treasurer General: Dr S. J. Rottman
Hon. Membership Secretary: Dr W. S. A. Gunn

WORLD FEDERATION OF SOCIETIES OF ANAESTHESIOLOGISTS

The World Federation of Societies of Anaesthesiologists (WFSA) was formally constituted at the First World Congress of Anaesthesiologists in Scheveningen and the Hague in 1955. There were 28 founder member societies. The Federation now has 98 member societies.

Its objectives are:

(1) to assist and encourage the formation of National Societies of Anaesthesiologists;
(2) to promote education and the dissemination of scientific information;
(3) to arrange, at regular intervals, a World Congress of Anaesthesiologists and sponsor Regional Congresses; to encourage meetings of special interest groups within the speciality and make provision for them to meet where appropriate at the above Congresses;
(4) to recommend desirable standards for the training of anaesthesiologists;
(5) to provide information regarding opportunities for postgraduate training and research;
(6) to encourage research into all aspects of anaesthesiology;
(7) to encourage the establishment of safety measures including the standardization of equipment;
(8) to advise, upon request, national and international organizations;
(9) to apply all other lawful means which may be conducive to the objects of the Federation.

The Federation has a President, a Secretary and a Treasurer and an Executive Committee. A General Assembly consisting of official delegates of all member societies is held every four years at the time of the World Congress.

The WFSA also has regional sections. The European Regional Section and the Asian/Australasian Section each hold congresses every four years. The Confederation of Latin-American Societies of Anaesthesiologists (CLASA) is also a regional section of WFSA and holds congresses in alternate odd years. Future congress venues are as follows:

World Congresses	*European Congresses*
1996 Sydney	1994 Jerusalem
2000 Montreal	1998 Berlin
2004 Paris	

Asian/Australasian Congresses	*CLASA Congresses*
1994 Bangkok	1993 Bogota, Colombia
1998 Taipei	

The WFSA is a recognized Non-Governmental Organization of the World Health Organization (WHO) with whom it worked closely in establishing anaesthetic training centres in Caracas and Manila.

WFSA publications include a twice-yearly Newsletter which is published in English, French, German and Spanish. There is also an Annual Report which combines a Directory of Member Societies, a Committee Address Book and an International Congress Calender into one booklet.

The Federation has published two low-cost handbooks—*Obstetric Anaesthesia and Analgesia* and *Paediatric Anaesthesia*—both of which are available from the Secretary. The Federation also supports *Anaesthesia—Update*, an add-on publication intended for the developing world, and has helped develop a basic anaesthetic manual, *Anaesthesia at the District Hospital*, in conjunction with the WHO. It has helped fund *Intensive Care in the Tropics*.

The WFSA funds an educational programme which has either initiated or supported intensive courses in East and West Africa, Fiji and the former USSR.

All enquiries should be directed to: Professor M. D. Vickers, Department of Anaesthetics, UWCM, Heath Park, Cardiff CF4 4XN. Tel. 0222 743110; Fax 0222 747203.

Current Officers:

WFSA (until April 1996)

President:	Dr Saywan Lim (Kuala Lumpur, Malaysia)
Secretary:	Professor M. D. Vickers (Cardiff, U.K.)
Treasurer:	Dr M. Rosen (Cardiff, U.K.)
Chairman, Executive Committee:	Dr B. V. Wetchler (Peoria, U.S.A.)
Vice-Chairman, Executive Committee:	Professor T. C. K. Brown (Melbourne, Australia)

Armed Services

ARMED FORCES

The Joint Services Anaesthetic Equipment Standardization Working Party (JSAESWP) has two functions. It deals largely with the standardization of equipment and policies. It is responsible to the Surgeon General and represents the speciality of anaesthetics within the Forces.

The Committee also sits as a Speciality Board to formulate policy on all aspects of postgraduate education in consultation with the appropriate committees of the Royal College of Anaesthetists. The chairman rotates between the three services on a three-yearly basis, and is *ex officio* co-opted onto the Council of the Association of Anaesthetists. Since 1983 the service Consultant Advisers have been "Regional Education Advisers for their Service" and are members of the College Education Advisory Panel.

The current chairman of the JSAESWP and Speciality Board is Brigadier J. Restall, Consultant Adviser in Anaesthetics and Resuscitation, Cambridge Military Hospital, Aldershot, Hampshire GU11 2AN. Tel. 0252-348232.

The two other members, who are Consultant Advisers in Anaesthetics for their respective services are: Surgeon Commander I. F. Geraghty, RN, Royal Naval Hospital, Haslar, Gosport, Hants PO12 2AA. Tel. 0705-584255 (ext. 2422); and Wing Commander I. Spencer, RAF, Central Medical Establishment, Kelvin House, Cleveland St, London WC1P 6AU. Tel. 071-636 4651; Fax 071-323 5937.

SOCIETY OF NAVAL ANAESTHETISTS

The Society of Naval Anaesthetists was founded in 1984 to promote good relationships between anaesthetists who are at present, or have been in the past, associated with the Royal Navy. At present the membership is well over 100. A biennial scientific meeting is held followed by a dinner in the evening. The venue alternates between Gosport (near Portsmouth) and Plymouth.

Membership is open to all anaesthetists who have a past or present association with the Royal Navy.

Details can be obtained from: Surgeon Commander I. F. Geraghty, Department of Anaesthetics, Royal Naval Hospital, Haslar, Gosport, Hants PO12 2AA. Tel. 0705-584255 (ext. 2422).

TERRITORIAL ARMY MEDICAL SERVICES

A Medical Officer in a local Independent Unit in the Territorial Army Medical Services attends a minimum of six weekend exercises, a 2-week summer camp and some weekday evenings. Alternatively, a Specialist Unit meets for two training weekends and a 2-week summer camp. If your circumstances change it is possible to alternate between the two units. An annual commitment of only 1 week is offered to anaesthetists who are unable to join the Specialist Unit. Members are paid the equivalent rates to the Regular Army, in addition to an annual tax free bonus. The Queen's Commission is awarded to all members.

For further information contact: Miss A. P. Frayer, T.A. Medical Services Specialist Recruiter, Keogh Barracks, Ash Vale, Aldershot GU12 5RQ. Tel. 0252-24431 (ext. Keogh Mil 5224).

TRI-SERVICE ANAESTHETIC SOCIETY

The inaugural meeting of the Tri-Service Anaesthetic Society was held at the Royal Army Medical College on June 30, July 1, 1989. The final meeting of the Society of Anaesthetists, British Forces Germany was held at the British Military Hospital, Iserlohn on September 26, 1992. A resolution was passed incorporating the Society of Anaesthetists, British Forces Germany into the Tri-Service Anaesthetic Society.

Membership of the Tri-Service Anaesthetic Society is open to all anaesthetists serving in the regular, volunteer or reserve forces. Membership is open to other interested persons by invitation. The aim of the Society is to promote the specialty of military anaesthesia, to educate and to act as a forum for a common interest in trauma life support and field anaesthesia. Further information can be obtained from Brigadier J. Restall.

The next meeting will be held in the Royal Army Medical College, Millbank, London SW1P 4RJ on Friday, November 12, 1993. Further information on this meeting can be obtained from: Major W. A. McFadzean, Department of Anaesthetics, Cambridge Military Hospital, Aldershot, Hants GU11 2AN. Tel. 0252-348336.

National Specialist Societies

AGE ANAESTHESIA ASSOCIATION

The Association, formed in March 1987, exists to promote the art and science of anaesthesia for old age patients, and to provide a forum for discussion and research of pertinent matters.

Ordinary members are elected from registered medical practitioners engaged in the practice of anaesthesia, and other registered medical practitioners in allied specialties.

Retired members are elected from those ordinary members who have retired from active practice. Honorary life members are elected from persons, nominated by Council, who have made outstanding contributions to the advancement of anaesthesia and allied specialties, and upon whom the Society desires to confer recognition by the presentation of a certificate at an annual general meeting.

Associate members may be elected from persons practising in any related field, but would have no voting right.

Meetings are held prior to Easter throughout the United Kingdom and are hosted by a local member. Speakers are invited to contribute papers on a chosen theme. An eminent contributor to any field in the care of the elderly is invited to be the Wyeth Guest Lecturer. At a Workshop session short papers with a limit of 15 minutes for presentation and discussion allow members to present work. Membership at the beginning of 1991 stands at 218. No membership fee is required, but a registration fee is payable by members attending meetings.

For further information contact: Dr W. G. B. Clark, or Dr G. A. H. Heaney, Hon. Membership Secretary, Department of Anaesthesia, Good Hope Hospital, Sutton Coldfield, West Midlands B75 7RR. Tel. 021-378 2211 (ext. 2428).

Current Officers:

President:	Dr M. Dodson
Hon. Secretary:	Dr C. J. Knickenberg
Hon. Membership Secretary and Treasurer:	Dr G. A. H. Heaney

ANAESTHETIC RESEARCH SOCIETY

In 1958, a small group of individuals interested in research in anaesthesia joined to form the Anaesthetic Research Group. With expansion of interest, the membership of the group increased and in 1968, the name was changed to the Anaesthetic Research Society.

The Society holds meetings three times a year in the U.K. for the presentation, discussion and encouragement of original research in anaesthesia and related subjects. Its affairs are now regulated by an Executive Committee of eight members including a Chairman, Secretary and Treasurer. Since 1964 abstracts of work presented to the Society have been published in the *British Journal of Anaesthesia.*

Membership of the Society is by election by ordinary members and open to anyone interested in anaesthesia or related research. There are approximately 650 members. Temporary membership is available for a maximum of three years. Ordinary membership is granted only to those who have presented a paper to the Society. Honorary members are persons of distinction who have made notable contributions to the advancement of anaesthesia by research.

For further information contact: Dr J. M. Hunter, Hon. Secretary, Anaesthetic Research Society, University Department of Anaesthesia, Royal Liverpool University Hospital, Prescot Street, P.O. Box 147, Liverpool L69 3BX. Tel. 051-706 4000; Fax 051-706 5815.

Current Officers:

Chairman:	Professor A. P. Adams
Hon. Secretary:	Dr J. M. Hunter
Hon. Treasurer:	Dr G. B. Drummond

ASSOCIATION OF CARDIOTHORACIC ANAESTHETISTS

The Association of Cardiothoracic Anaesthetists (ACTA) was founded in 1984. Its aim is to hold regular meetings about topics of interest to anaesthetists practising cardiac or thoracic anaesthetics and to encourage those training who have an interest in this speciality. ACTA organizes two meetings a year, one in Cambridge and one elsewhere. The inaugural meeting of the European Association of Cardiothoracic Anaesthetists was held in conjunction with the Association in 1986.

Membership is approximately 250 and is open to consultant anaesthetists in Great Britain and Ireland who have a commitment to cardiac or thoracic anaesthesia.

Further information can be obtained from: Dr R. Feneck, Hon. Secretary ACTA, London Chest Hospital, Bonner Road, London E2 9JX. Tel. 081-980 4433.

Current Officers:

Hon. Secretary:	Dr R. Feneck
Hon. Treasurer:	Dr R. D. Latimer

ASSOCIATION OF DENTAL ANAESTHETISTS

In November 1976 the formation of an association of dental anaesthetists was discussed publicly for the first time and on 16 April 1977 the inaugural meeting was held in Manchester.

The aims of the Association of Dental Anaesthetists (ADA) are to further the art and science of anaesthesia and sedation for dentistry and to provide a forum for discussion.

Membership is open to medical or dental practitioners with an interest in dental anaesthesia, sedation or analgesia who have been approved by Council. Under exceptional circumstances members have been approved who are not medically or dentally qualified. Currently there are approximately 400 members including 20 members from overseas.

Meetings are held twice a year; in January a one-day meeting is held in London and in June a one- or two-day meeting is held elsewhere. In 1988 a three-day meeting was held jointly with the European Federation for the Advancement of Anaesthesia in Dentistry (EFAAD). The ADA is a member of EFAAD and sends a representative to its council meetings. The proceedings of the meetings are published annually and during 1990 guidelines on monitoring during dental anaesthesia and sedation were published.

Further information can be obtained from: Dr P. B. Hewitt, Department of Anaesthetics, Guy's Hospital, London SE1 9RT. Tel. 071-955 4051/5000.

Current Officers:

President:	Mr R. C. Bret Day (London)
Hon. Secretary:	Dr P. B. Hewitt
Assistant Hon. Secretary/Editor:	Miss A. M. Skelly (Guy's Hospital)
Hon. Treasurer/ Membership Secretary:	Dr A. Padfield (Sheffield)

ASSOCIATION OF PAEDIATRIC ANAESTHETISTS (GREAT BRITAIN AND IRELAND)

The Association of Paediatric Anaesthetists (APA) was founded in 1973, when a small group of interested individuals met in Bristol. Since then the membership has increased to over 200, including many overseas anaesthetists from all major countries.

The Association holds an Annual Scientific Meeting in March every year, and joint meetings with other similar societies, often abroad. Postgraduate seminars are also organized.

The aims of the Association are to further the study of the practice and science of paediatric anaesthesia; to encourage the proper teaching and training of anaesthetists in the subject; and to provide a forum for discussion by its members.

Membership is open by election to consultant anaesthetists in Great Britain and Ireland whose main commitment is to paediatric anaesthesia or who have demonstrably contributed to the aims of the Association. Membership is also open to a limited number of paediatric anaesthetists from overseas. Applications may be proposed by any member of the Association. A year book is published for members of the APA.

The APA communicates closely with the Association of Anaesthetists, and is represented on a Liaison Committee with the British Paediatric Association and the British Association of Paediatric Surgeons.

Further information can be obtained from: Dr D. S. Arthur, Hon. Secretary, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ. Tel. 041-339 8888.

Current Officers:

President:	Dr P. Morris
President Elect:	Professor D. Hatch
Hon. Secretary and Treasurer:	Dr D. S. Arthur

BRITISH ASSOCIATION FOR IMMEDIATE CARE (BASICS)

The British Association for Immediate Care (BASICS) was formed in 1977, following pioneering work begun by Dr Ken Easton O.B.E. Immediate care is defined as the provision of skilled medical help at the scene of an accident, medical emergency or during transportation to hospital.

Doctors throughout the United Kingdom have organized themselves voluntarily to provide such immediate care either as individuals or through Immediate Care schemes. At present, approximately one-third of the United Kingdom is covered by 99 schemes involving 1850 doctors, in addition to 500 individual members and 410 associate members. Individual and scheme membership is open to medical practitioners and associate membership is open to all others interested in immediate care.

The aims of BASICS are to foster co-operation between existing Immediate Care schemes and to encourage and aid the formation and extension of schemes in the United Kingdom; to develop and strengthen co-operation between all services in dealing with emergencies; to encourage and assist research into all aspects of immediate care and accident prevention; to raise the standards of immediate care training; to produce publications for the dissemination of information; and to evaluate specialist emergency equipment.

The Association is governed by its Council and Officers elected by the membership. Various committees have been set up to pursue the aims of BASICS and currently cover Inter Service Liaison and Disaster Planning, Research and Development, Radio Communications, Equipment, and Journal Publications and Education. There are also Scottish, Welsh and Northern Ireland sections. Representatives of the emergency services and other organizations involved in emergency care participate in the committees.

BASICS is registered as a charity and has therefore to rely on its membership and the public for financial support.

Enquiries should be directed to Mr R. Bailey, Chief Executive, BASICS, 7 Black Horse Lane, Ipswich, Suffolk IP1 2EF. Tel. 0473-218407; Fax 0473-280585.

HISTORY OF ANAESTHESIA SOCIETY

Following an exploratory meeting in 1985, the Society was founded in 1986 of a group of mainly anaesthetists with an interest in the history of anaesthesia.

Meetings are held twice a year for the presentation of papers concerned with the history of anaesthesia and related subjects. The Society's proceedings are published following each meeting.

The Society is run by a Council made up of six officers and a majority number of elected members. The officers are President, Vice-President, Membership Secretary and Treasurer, Editor and Honorary Secretary.

Membership of the Society is by election for ordinary members and is open to anyone interested in the history of anaesthesia. The membership number now stands at well over 300 of which most are anaesthetists with a number of other practitioners including dentists, ODAs, engineers and medical historians from all over the world.

The Society co-ordinates also with other bodies, both within the United Kingdom and overseas, concerning topics of interest to anaesthetic historians.

For further information contact: Dr I. McLellan, Hon. Secretary, History of Anaesthesia Society, Department of Anaesthesia, Groby Road Hospital, Groby Road, Leicester LE3 9QE. Tel. 0533-874 141 (ext. 488).

Current Officers:

President:	Dr A. K. Adams
Vice-President/ President Elect:	Dr D. D. C. Howat
Hon. Treasurer/ Membership Secretary:	Dr A. Padfield
Editor:	Dr D. Wilkinson
Hon. Secretary:	Dr I. McLellan
Assistant Hon. Secretary:	Dr A. Bennett

INTENSIVE CARE SOCIETY

The Intensive Care Society was founded in 1970 to bring together clinicians involved in intensive care. Membership currently stands at around 925 including 40 overseas members. The Society encourages a multidisciplinary membership and includes physicians, surgeons, clinical physiologists and pathologists, although the majority are

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anaesthetists. All grades of medical staff are eligible for membership and a limited number of non-medical workers may also join.

Ten Council members are elected to run the Society. Council members serve for a period of three years and may stand for a second term. By constitution, only seven of the 10 members may be practising anaesthetists. H.R.H. The Princess Royal is the Patron of the Society.

There are two scientific meetings each year open to members and their guests. Free papers are selected for presentation at both meetings. The Annual General Meeting of the Society is held during the Autumn Meeting. Details of these and the Society's other activities are published in the twice-yearly Newsletter. The Society has also published *Standards for Intensive Care Units; Intensive Care Audit; Fire Safety in the Intensive Care Unit* and *The Intensive Care Service in the U.K.* which have proved a valuable source of information for those involved in the provision of intensive care.

The Society is a founding member of the World Federation of Societies of Intensive and Critical Care Medicines and has close links with the European Society of Intensive Care Medicine.

Two Travelling Fellowships are available annually for clinicians who wish to visit other intensive care units. The Society has also funds available to support research and other relevant activities. An appeal was launched in 1989 so that the Society could play a more active role in encouraging research in all aspects of intensive care.

Subscription is currently £50 for consultant members and £25 for junior, overseas and retired members. The Society is a registered charity.

Further information is available from: Alasdair Short, Hon. Secretary, Intensive Care Society, 9 Bedford Square, London WC1B 3RA. Tel. 071-631 1650.

Current Officers:

President:	Dr M. S. Neilsen
Hon. Secretary/Treasurer:	Dr A. Short
Meetings Secretary:	Dr P. Lawler

NEUROANAESTHETISTS' TRAVELLING CLUB OF GREAT BRITAIN AND IRELAND

In the late 1950s the Scottish Neurosurgical Anaesthetists met informally in each others' homes to discuss neuroanaesthesia. At that time there was a great explosion of knowledge concerning the physiological factors which determine intracranial pressure and affect cerebral blood flow under anaesthesia, and there was much interest in the application of techniques for inducing hypotension for intracranial surgery. In the early 1960s these anaesthetists met with their colleagues in Newcastle, and in 1965 Dr A. R. Hunter of Manchester invited anaesthetists with a special interest in neuroanaesthesia to a scientific meeting in Manchester and the Neurosurgical Anaesthetists' Travelling Club of Great Britain and Ireland came into existence.

Membership of the Travelling Club is open to any consultant or doctor with equivalent status who devotes a major part of his or her time to neuroanaesthesia. This regulation is interpreted quite liberally and there are basic scientists and neurosurgeons who are members of the Travelling Club. There are also overseas members of the Club, and the total membership of the Club at present is 215.

There is an annual scientific meeting which is open to members and non-members alike. The venue for these meetings "travels" from one neuroanaesthetic centre to another, hence the name Travelling Club. The A. Harvey Granat Memorial Prize is awarded annually to the junior anaesthetist who gives the best presentation at the annual scientific meeting. In addition to the annual meeting, combined meetings with overseas neuroanaesthetists are frequently arranged. On alternate years the McDowall Trustees arrange for the McDowall Memorial Lecture to be presented at the annual scientific meeting.

The Travelling Club has always valued its informality and continues to do so. There is no annual membership fee, no constitution, no council, and the general running of the Travelling Club is left to the Honorary Secretary.

Further details of all the meetings and an application form for membership can be obtained from: Dr J. L. Jenkinson, Hon. Secretary, Neuroanaesthetists' Travelling Club of Great Britain and Ireland, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU. Tel. 031-332 2525 (ext. 4786); Fax 031-332 5150.

OBSTETRIC ANAESTHETISTS ASSOCIATION

The Obstetric Anaesthetists Association (OAA) was founded in 1969 by a small group of anaesthetists concerned with raising the standards of obstetric anaesthesia in the United Kingdom. The object of the Association is to promote the highest standards of management and care for mother and baby in every aspect of anaesthetic practice. As a result of its discussions, the OAA has produced a series of considered views on various aspects of anaesthesia and analgesia in obstetric units. These views have been embodied in evidence presented to various committees and working parties, most notably the Social Services Select Committee.

Meetings of the Association are held twice a year, in March and September in different centres in the United Kingdom and are hosted by a local member of the OAA. Approximately every three years a meeting is held at a centre elsewhere in Europe. The meetings of the Association are usually one day. As well as providing the opportunity for the presentation of papers on various aspects of obstetric anaesthetic and analgesic practice and its associated problems, the meetings provide an opportunity for meeting colleagues to discuss common problems and exchange ideas. The Annual General Meeting of the Association is incorporated into the Spring Meeting of the Association.

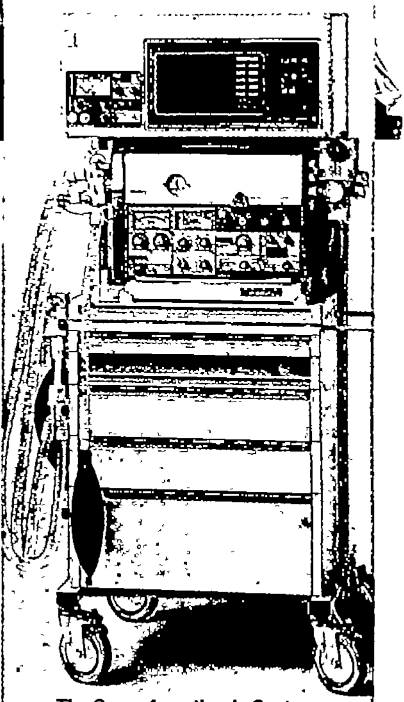
The OAA Gold Medal is presented occasionally to an individual judged to be pre-eminent in the speciality and is presented at a meeting of the Association when the person concerned gives a lecture.

The OAA is prepared to make financial grants to members in support of research activities. Applications for such support should be made in the first instance to the Honorary Secretary. The Association has also initiated a Junior Obstetric Anaesthetists prize awarded annually to an anaesthetist in training for a short paper, either a review or original work not previously published, to be presented at the Spring Meeting of the OAA. Entries for this prize should be made in manuscript form to the President of the Association not later than 30 September each year.

Full membership is open to medical practitioners in the United Kingdom and overseas. Associate membership is granted at the discretion of the Committee to non-medically qualified persons who share the objectives of the Association. The OAA has flourished since its inception and there are over 1000 United Kingdom members and 200 overseas members. A handbook is published usually every other year and circulated to members, giving details of the Constitution, the Committee and an address list of members.

Information concerning future meetings, changes in officers and members of the Committee are presented in

SIEMENS



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Details of membership and application forms can be obtained from: Dr R. J. S. Birks, Hon. Secretary, Department of Anaesthesia, Jessop Hospital for Women, Leavygreave Road, Sheffield S3 7RE. Tel. 0742-766333; Fax 0742-701403.

Current Officers:
President: Dr L. E. S. Carrie (Oxford)
Hon. Secretary: Dr R. J. S. Birks (Sheffield)
Hon. Treasurer: Dr R. Verma (Derby)

PAEDIATRIC INTENSIVE CARE SOCIETY

The Paediatric Intensive Care Society (PICS) was founded in 1987 as a multidisciplinary group for those interested and involved in paediatric intensive care. Its aims are to provide a forum for discussion and specialist advice, to stimulate research and collaborative studies, to promote training and education and to collect information through the Council of the Society.

Membership is open to persons actively involved in paediatric intensive care or involved in work contributing to the paediatric intensive care field.

The eight members of the Council consist of three nursing representatives, two paediatricians, two paediatric anaesthetists and one paediatric surgeon.

The Society holds two meetings a year.

Further information may be obtained from: Dr Jane Ratcliffe, Hon. Secretary, Paediatric Intensive Care Society, Royal Liverpool Children's Hospital, Alder Hey, Eaton Road, Liverpool L12 2AP. Tel. 051-228 4811; Fax 051-228 0328.

Current Officers:
Chairman: Dr Neil Bennett
Hon. Secretary: Dr Jane Ratcliffe
Hon. Treasurer: Mrs Carol Levy
Meetings Secretary: Mrs Julie Asquith

PAIN SOCIETY

The Intractable Pain Society of Great Britain and Ireland was founded in 1967, the first Society concerned with the clinical management of chronic pain. Membership was limited primarily to clinicians who ran Pain Clinics but the Society included consultant psychiatrists, neurosurgeons and neurologists. It has in recent years expanded to become the Society for all those involved with research into and the management of pain in all its aspects. The Society is now the British and Irish Chapter of the International Association for the Study of Pain and has 550 members.

The Society produces a biannual journal—*Journal of the Pain Society of Great Britain and Ireland*. Together with the Pain Relief Foundation in Liverpool, the Society has awarded a Travelling Fellowship of £1000 and a Research Grant of £10 000.

The Annual Meeting of the Society is held at a different centre every year. The Society also has arrangements with Pain Societies in other countries so that meetings are often held abroad. In addition to national meetings, regional meetings are held by regional groups.

The Society has recently set up a register of senior registrars interested in a career in chronic pain relief so that those departments wishing to appoint a consultant will have some information concerning the availability of applicants for such a post.

More information about the Society and applications for membership may be obtained from: Dr C. L. Knight, Hon. Secretary, Pain Society of Great Britain and Ireland, 9 Bedford Square, London WC1B 3RA. Tel. 071-631 1650.

Current Officers:
President: Dr A. W. Diamond
Hon. Secretary: Dr C. L. Knight
Hon. Treasurer: Dr D. Justins
Editor Pain Society Journal: Dr R. Johnson

PLASTIC SURGERY AND BURNS ANAESTHETISTS

The Society was formed in 1982 when a group of anaesthetists interested in plastic surgery and burns patients met in Nottingham. Initially the meetings were held biennially but with increasing interest it was decided, in 1986, to meet on an annual basis. In 1989 the Society was formally registered as a charity with the Charity Commissioners.

The annual meeting of the Society is held in the United Kingdom in the Autumn at different sites involved in plastic surgery and burns therapy. At the annual meeting the Russell Davies-Stuart Laird Prize (named after two pioneers of anaesthesia in this field), generously donated by Abbott Laboratories, is awarded following presentation of work related to anaesthesia for plastic surgery or burns. It is valued at £200. The affairs of the Society are conducted in a relatively informal manner with three permanent officers—the President, Secretary and Treasurer—and a Meetings Organizer who hosts the annual meeting and changes with each venue.

Membership of the Society is open to all anaesthetists in the United Kingdom who are involved and interested in the care of burn patients and those requiring plastic surgery.

Information on the Society can be obtained from: Dr K. C. Judkins, Secretary PSBA, The Anaesthetic Department, Queen Victoria Hospital, East Grinstead, West Sussex RH19 3DZ. Tel. 0342-410210; Fax 0342-317907.

Current Officers:
President: Dr V. A. Goat
Hon. Secretary: Dr K. C. Judkins
Hon. Treasurer: Dr C. Tolhurst-Cleaver

RESEARCH DEFENCE SOCIETY

The Research Defence Society was founded in 1908 to educate and inform the general public about the use of animals in biological and medical research, the many benefits which have come from such research and the regulations concerning laboratory animal welfare under which such research is conducted. To achieve these aims the Society provides information to the media, universities, school students and the general public and monitors and responds to anti-vivisection propaganda. A close liaison with the media ensures that speakers are available to take part in debates, discussion programmes, documentaries etc. The Society publishes a quarterly Newsletter as well as numerous public education leaflets and booklets.

The Society maintains a liaison with industry, academia and the government on issues relevant to biomedical research involving animals and, where appropriate, seeks to influence any proposal to vary relevant legislation or codes of practice.

The Society advises its members regarding any problems associated with the use of animals in research and works actively to stimulate improvements in the conditions in which laboratory animals are maintained and the standards of the research in which they are used.

Membership of the Society is currently 6500 and is

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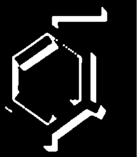

open to any person who supports the objectives of the Society.

Further information can be obtained from: Dr Mark Matfield, Executive Director, Research Defence Society, 58 Great Marlborough Street, London W1V 1DD. Tel. 071-287 2818; Fax 071-287 2627.

Current Officers:

Chairman:	Dr D. Jack
Hon. Treasurer:	Dr J. F. Cavalla
Hon. Secretary:	Professor R. Guillary

RESUSCITATION COUNCIL (U.K.)

In 1982 a small group of interested doctors formed the Resuscitation Council (U.K.) (formerly the Community Resuscitation Advisory Council) with the specific objectives of: saving life by the education of the public and improving the education of medical practitioners, nursing, ambulance and other health workers in resuscitation procedures; and investigating, encouraging and conducting research into methods of resuscitation and the dissemination of the useful results of such research.

In 1986 the Council produced its first complete set of national recommendations for resuscitation, the *ABC of Resuscitation* (Editor Dr T. R. Evans) which was published by the *British Medical Journal*. A second edition containing revised schedules, including more resuscitation disciplines, was published in early 1990. The Council has also published a series of posters and leaflets on resuscitation which have proved to be extremely popular amongst medical, nursing and paramedical staff and the general public. In 1986 the Council commenced a national survey of resuscitation results of patients requiring resuscitation within the hospital. The conclusions of this survey were published in 1990.

The Council is composed of an Executive Council consisting of a total of 21 elected members, and an ordinary membership of the General Council. In 1989, the Council expanded its ordinary membership to include those nominated and sponsored by two ordinary members of the Council. Membership is open only to medical practitioners registered by the General Medical Council of the United Kingdom who have demonstrated a special interest or expertise in the field of resuscitation. The Council regards itself as multidisciplinary and recruits members from a wide variety of disciplines within the medical practice.

Further information can be obtained from: Dr A. J. Handley, Hon. Secretary, Resuscitation Council (U.K.), Colchester General Hospital, Turner Road, Colchester, Essex CO4 5JL. Tel. 0208-832453 (ext. 2453); Fax 0206-854327.

Current Officers:

Chairman:	Dr C. Robertson
Hon. Secretary:	Dr A. J. Handley
Hon. Treasurer:	Dr M. Ward

SOCIETY FOR COMPUTING AND TECHNOLOGY IN ANAESTHESIA

The Society was founded as The Computing in Anaesthesia Society in 1987, to provide a forum for those interested in any application of computing in anaesthesia. Although the founders were originally interested in record keeping and audit, the interests of members range from drug distribution modelling to the logic and reliability of monitors. For this reason we subsequently changed the name to include technology.

The Society has approximately 150 members and holds meetings in May and November each year. The subscription is £10 per year. The constitution of the Society includes research and education amongst its aims and it is therefore pleased to offer the Association of Anaesthetists a research grant to sponsor a relevant project and offers a visiting Fellowship for anaesthetists in training from abroad to study in the U.K.

The Society has become aware of the need for the profession to work more closely with industry. We have felt for some time that the profession is not getting equipment designed in the way that it requires, and that business is not getting guidance from the profession on the priorities that are important to them. This problem applies across the whole range of anaesthetic instrumentation, from anaesthetic machines to monitoring equipment and record keeping systems. Therefore we have incorporated industrial members of the Society who participate fully in meetings.

In 1989 the Society cloned a European sibling, the European Society for Computing and Technology in Anaesthesia and Intensive Care, which meets annually in October.

For further information contact: Dr M. Stuart-Taylor, Secretary, Anaesthetic Department, Odstock Hospital, Salisbury, Wiltshire SP2 8BJ. Tel. 0722-336262 (ext. 2051); Fax 0722-414143.

SOCIETY OF ANAESTHETIC LABORATORY TECHNOLOGISTS

The Society of Anaesthetic Laboratory Technologists was founded in October 1970 and the first formal meeting was held in Birmingham in April 1971. The aim of the Society is to further the speciality of anaesthesia by:

(1) Promoting liaison between laboratory technologists employed in Departments of Anaesthesia.
(2) Providing opportunity for discussion and presentation of information on technical and academic matters associated with anaesthesia.
(3) Co-ordinating the training of anaesthetic laboratory technologists and promoting recognized qualifications.
(4) Advising on the career structure of laboratory technologists in Departments of Anaesthesia.

The qualifications for membership reflect the wide range of expertise required by technologists working in anaesthesia and provide four grades of membership. *Student Member*: A technologist undergoing an initial course of approved training and study whilst employed in an Anaesthesia Department Laboratory. *Member*: A technologist having the qualification of Technical Education Council Certificate or equivalent (O.N.C., etc.) in an approved subject and who has been employed in an Anaesthetic Department Laboratory for at least 12 months. *Fellow*: A technologist having the qualification of Technical Education Council Higher Certificate or equivalent (H.N.C., etc.) in an approved subject, and who has been employed in an Anaesthetic Department Laboratory for at least five years after obtaining his/her qualifications. Election of Fellowship is by application and approval of the Committee. *Associate Member*: Associate Membership should be granted at the Committee's discretion to: (i) fully paid up members or fellows who by virtue of their change of employment are no longer eligible for normal membership; (ii) technologists employed in allied disciplines; (iii) members of the Society who at the time of their retirement are still employed in an Anaesthetic Laboratory environment should be granted life membership. *Overseas Members*: Technologists who have qualifications in accordance with the membership qualifications given above may, at the discretion of the Committee, be granted membership in the appropriate grade.

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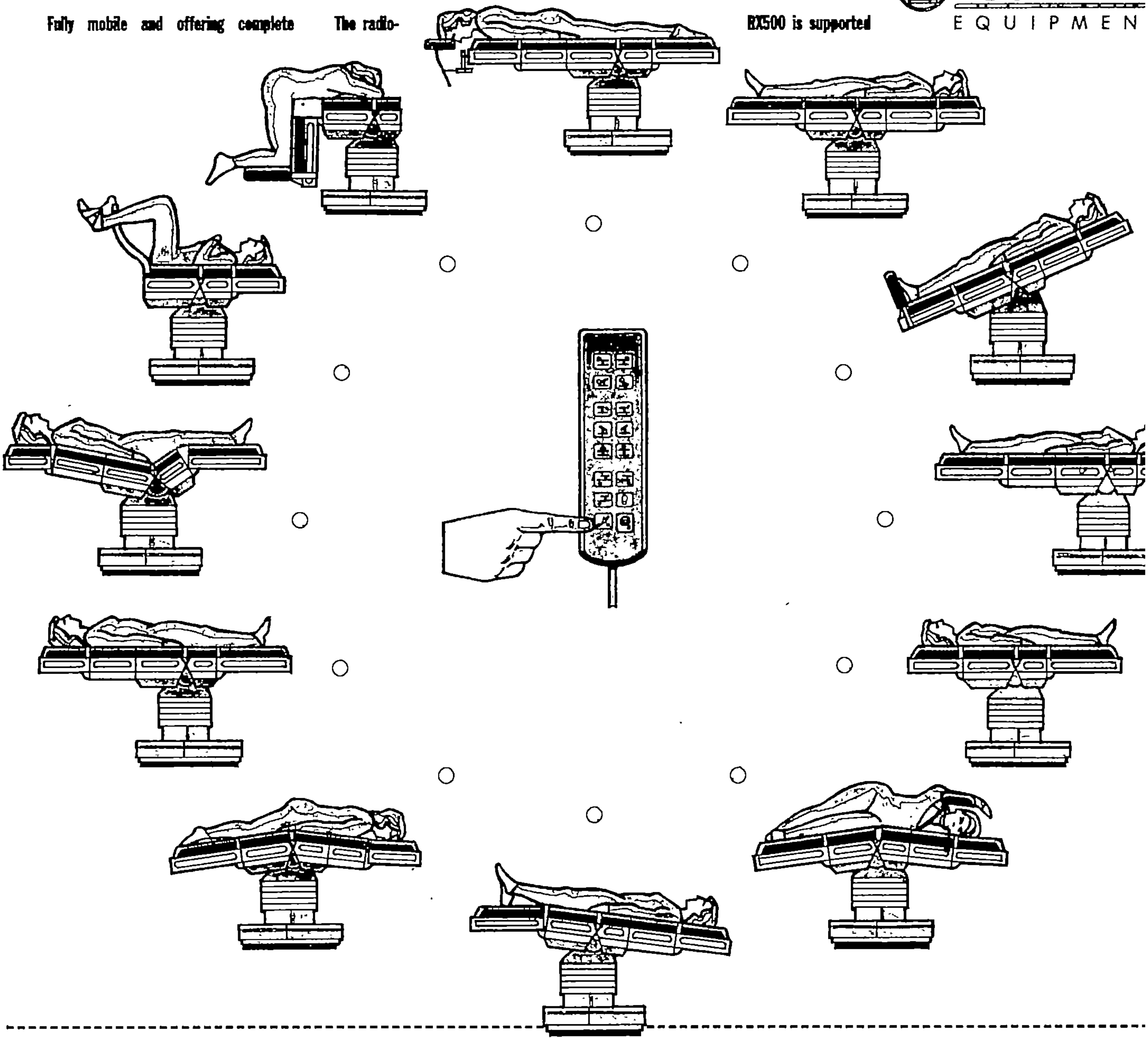

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laboratory science, clinical or physiological measurement, medical physics and mechanical or electronic engineering.

Scientific meetings are held twice a year at different centres when members are given the opportunity to read papers on aspects of their work. The Ken Hillard Memorial Prize is presented at each meeting to the member who, in the Chairman's opinion, presents the best paper.

A Newsletter is circulated by the Secretary between meetings. In 1976 the Society established a Guest Lecture to commemorate the retirement of Richard Salt. Provision is made for the Richard Salt lecture to be presented at a Society meeting every two years.

The Society is a member of the Federated Association of Medical Technology (FAMT). Representatives of the Society are sent to meetings and seminars of FAMT which provides opportunities for discussion between societies and organizations whose members are employed in the medical field and representatives of the Department of Health. There are currently 60 members of the Society.

For further information contact: Mr P. Sterling, Hon. Secretary, Society of Anaesthetic Laboratory Technologists, University Department of Anaesthesia, Royal Victoria Infirmary, Newcastle-upon-Tyne NE1 4LP. Tel. 091-222 6000 (ext. 8862).

Current Officers:

Chairman:	Mr R. Howard, M.B.E. (Gosport)
Hon. Secretary:	Mr P. Sterling (Newcastle-upon-Tyne)
Vice-Chairman:	Mr F. West (Liverpool)
Hon. Treasurer:	Ms M. A. Keegan (Manchester)
Education Officer:	Mr D. A. Morris (Oxford)

Regional and Local Anaesthetic Societies

ANGLIAN PAIN SOCIETY

The Society was formed in 1990 and aims to meet members' needs for exchange of scientific information, as well as political support, and fellowships meetings are held twice yearly in a convenient central location in the region.

The Society is run by:

Dr D. Hughes, Pain Relief Service, Addenbrooke's Hospital, Hills Road, Cambridge, Cambs CB2 2QQ. Tel. 0223-245151.

Dr J. B. Skinner, Department of Anaesthesia, The Ipswich Hospital, Heath Road, Ipswich, Suffolk IP4 5PD. Tel. 0473-702006.

Dr W. G. Notcutt, Anaesthetic Department, James Paget Hospital, Lowestoft Road, Gorleston, Great Yarmouth, Norfolk NR31 6LA. Tel. 0493-452452.

BRISTOL ANAESTHETIC CLUB

The Bristol Anaesthetic Club was formed in 1968. Meetings of the Club rotate around the three main hospitals in the city—the Bristol Royal Infirmary, Frenchay Hospital and Southmead Hospital. Three meetings per year are held in each of these hospitals, and an additional annual meeting is held in Bath.

The Club meets on the first Wednesday in the month, commencing with an informal buffet supper at 19:00 during which members can meet the guest speaker and discuss topics of mutual interest. Supper is followed by the formal lecture.

The anaesthetic staff of the host hospital select and invite the speaker and organize the meeting. There is no annual subscription or club treasurer, each meeting being "self-financing". However, funds are obtained from hospital sources to pay an honorarium and travelling expenses for the guest lecturer.

There is no formal membership of the Club, which is open to all who are interested. The anaesthetists in Bristol and the surrounding area are circulated with details of a meeting approximately three weeks in advance. In addition, colleagues from other disciplines who might be interested in the lecture are invited to attend, as also are members of the nursing staff who work in anaesthetic or intensive care areas.

Bristol has the advantage of being situated near the intersection of two major motorways, and the meetings attract members from Gloucester and Cheltenham to the north, Wales to the west, Bath to the east, and Weston-super-Mare and Taunton to the south. It is usual for the attendance to be between 40–60, mostly consultant anaesthetists, but with a good proportion of anaesthetists-in-training and nursing staff.

For further information contact: Secretary of the Department of Anaesthesia at any of the above hospitals or Dr Paul G. N. Thornton, Consultant Anaesthetist, Sir Humphry Davy Department of Anaesthesia at Bristol Royal Infirmary, Bristol BS2 8HW. Tel. 0272-282163; Fax 0272-291498.

EAST ANGLIAN REGIONAL ASSOCIATION OF ANAESTHETISTS

The East Anglian Regional Association of Anaesthetists was formed in Cambridge in 1950. The objectives of the Association were: to protect the interests of all doctors practising the speciality in the region; to enable those practising the speciality to meet together; and to be instructional.

Meetings are held three times a year in different parts of the region and one meeting is designated for registrars to present papers. The Harold Youngman Medal is awarded to the presenter of the best paper.

A magazine is distributed to all members annually giving information on regional events, commenting on changes occurring in anaesthetic departments in the region and containing some material of academic interest.

All consultant and specialist anaesthetists in the region are eligible for membership for a nominal subscription, and all junior anaesthetists are welcome without subscription.

For further information contact: Dr C. Watsham, Hon. Secretary, 26 Hauxton Road, Little Shelford, Cambridgeshire CB2 5HJ. Tel. 0223-842638.

EDINBURGH AND EAST OF SCOTLAND SOCIETY OF ANAESTHETISTS

The inaugural meeting of the Edinburgh and East of Scotland Society of Anaesthetists was held in 1945. The late Dr John Gillies was prominent among the founder members. The Society promotes the broad development of anaesthesia locally. Scientific meetings are held monthly from October to April, on Tuesday evenings, in the very attractive hall of the Royal College of Surgeons of Edinburgh in Nicolson Street. There are currently 150 members.

In October each year a combined meeting is held with the Glasgow and West of Scotland Anaesthetists and the venue alternates between the two cities. One meeting each year is reserved for papers from members of the Society, but for other meetings speakers on subjects relating to anaesthetic practice may be invited from anywhere in the U.K. An Associate Members Prize, currently £150, is on offer each year for an original essay, scientific paper or item of anaesthetic equipment. As the highlight of the social activities, the Society holds an annual dinner where spouses and guests of the members are cordially welcomed.

For further information contact: Dr J. H. McClure, Hon. Secretary, Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW. Tel. 031-2292477 (ext. 4545); Fax 031-229 3337.

FEATHERSTONE SOCIETY OF TRAVELLING ANAESTHETISTS

The Featherstone Society of Travelling Anaesthetists was founded on 2 November 1987 and was named in honour of the memory of Dr Henry Featherstone, a prominent Birmingham anaesthetist (1919–1959) and founder and first president of the Association of Anaesthetists. The aims of the Society are to meet colleagues, often at some centre of repute, to present informal papers and discuss problems associated with anaesthesia of interest to the members and also to enhance the members' knowledge of the manufacture of anaesthetic equipment and anaesthetic and para-anaesthetic drugs and agents.

The Society meets two to four times per year and membership is limited and by invitation only.

For further information contact: Dr I. D. Hall, Department of Anaesthetics, Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Edgbaston, Birmingham B15 2TH. Tel. 021-4721311 (ext. 3327/6/5).

GLASGOW AND WEST OF SCOTLAND SOCIETY OF ANAESTHETISTS

The Glasgow and West of Scotland Society of Anaesthetists was founded in January 1946 at the instigation of a small group of Glasgow anaesthetists, one of whom, Dr A. C. Forrester, was to become Scotland's first Professor of Anaesthesia, and another a President of the Association of Anaesthetists (Dr H. H. Pinkerton). The aims of the Society are: to promote the development of this special branch of medicine in the area specified; to encourage friendship among anaesthetists in the West of Scotland; and to offer opportunities for the discussion of various aspects of anaesthetic practice. Representative and organizational functions have been taken on by other bodies.

The affairs of the Society are conducted by a Council elected by the members and membership is open to all hospital anaesthetists in the West of Scotland. Membership currently stands at approximately 300.

Five scientific meetings are held each session in the Royal College of Physicians and Surgeons of Glasgow, 234–242 St Vincent Street, Glasgow. The first meeting is held jointly with the Edinburgh and East of Scotland Society of Anaesthetists, alternately in Glasgow and Edinburgh; a dinner usually follows this gathering. One other meeting is devoted to papers presented by members of the Society, and at the final meeting the Society is addressed by the President. For the past few years there has also been an annual golf outing.

Information regarding the Society can be obtained from Dr W. G. Doherty, Hon. Secretary, Department of Anaesthetics, Stobhill General Hospital, Glasgow G21 3UW. Tel. 041-558 0111.

HICKMAN ANAESTHETIC SOCIETY

The Hickman Anaesthetic Society was formed in 1958 by a group of consultant anaesthetists in the Birmingham region. The objectives are: to honour the memory of Dr Henry Hill Hickman who lived and worked in the Midlands; to create a forum for the exchange of views both of scientific and political interest to anaesthetists; to be prepared to travel at least once a year to meetings with other societies both at home and abroad.

Ordinary meetings are held three or four times a year at various centres throughout the West Midland region. Speakers are quite often Society members, but at least once a year the Society entertains a distinguished guest speaker.

Membership is limited and is strictly by invitation. There are currently 28 members.

Further information may be obtained from: Dr J. M. Watt, Hon. Secretary, 36 Westfield Road, Edgbaston, Birmingham B15 3QG. Tel. 021-454 4843.

LIVERPOOL SOCIETY OF ANAESTHETISTS

The Liverpool Society of Anaesthetists was founded on 16 July 1930 by a small group of local practitioners which included R. J. Minnitt, the pioneer of the gas and air machine which carried his name. The objectives of the Society were to promote "fellowship, mutual help, encouragement, co-operation, professional discussion and scientific advance" among its members. It was also created to formulate and organize policy, and make recommendations for the furtherance of the work of the specialist anaesthetist. Membership was open to all practitioners holding an appointment in anaesthetics at a hospital within the Liverpool district.

Today, membership stands at some 150 anaesthetists drawn from an area extending beyond the boundaries of Merseyside and South West Lancashire to Bangor in North Wales and Crewe in Cheshire. All anaesthetists in training are encouraged to attend meetings and to submit original work in competition for the Society's Janssen Prize, awarded annually at a meeting set aside for presentation of the papers. The winner is also awarded a Forrest Medal in memory of the well-loved Dr Tom Forrest, who died during his presidential term in 1988.

Although preserving a separate identity, since its foundation the Society has maintained close links with the Liverpool Medical Institution. The magnificent building of the Institution provides the regular venue for meetings of the Society of Anaesthetists. A joint meeting on an educational topic of common interest is organized by the Society and incorporated into the programme of meetings held by the Institution throughout the academic year.

The regular meetings of the Society, six in each session, are held on Friday evenings between October and May and are followed by a buffet supper. The programme is designed to provide as much variety in the field of anaesthesia as possible, the aim being to stimulate interest rather than to provide formal education. In March, a joint meeting with the Anaesthetic Section of the Manchester Medical Society is held, the venue alternating between the two cities. Following dinner, a speaker from each Society presents a paper.

The affairs of the Society are managed by a committee comprising the President, three Vice-Presidents, an Honorary Secretary, an Honorary Treasurer, four ordinary members and a co-opted member of junior staff. Emeritus Professor T. Cecil Gray and Dr G. Jackson Rees maintain a watching brief over Society affairs as Vice-Presidents for life. The President, currently Professor J. E. Utting, holds office for two years, serving as Vice-President, (currently Dr A. A. Gilbertson) for one year on either side of his term of office as President. The ordinary members are eligible to serve for four years and are selected to cover all branches of the speciality. As far as is possible, peripheral hospitals and the University Department of Anaesthesia are represented.

For further information contact: Dr John Chambers, Hon. Secretary, Liverpool Society of Anaesthetists, Arrowe Park Hospital, Wirral, Merseyside L49 5LN. Tel. 051-678 5111 (ext. 2334).

MANCHESTER MEDICAL SOCIETY, SECTION OF ANAESTHESIA

The Manchester Medical Society was reconstituted in 1950 by the amalgamation of Medical, Pathological, Surgical, Anaesthetic and Odontological Societies. Most of the functions of the Manchester and District Society of Anaesthetists, which was founded in November 1945, are carried out by the Section of Anaesthesia of the Manchester Medical Society. The original organization,

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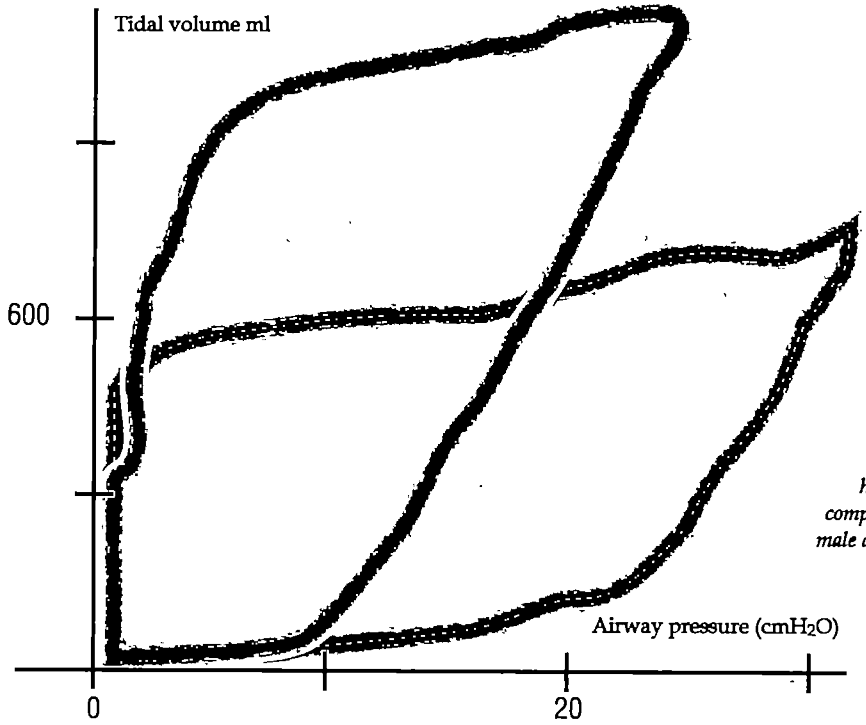

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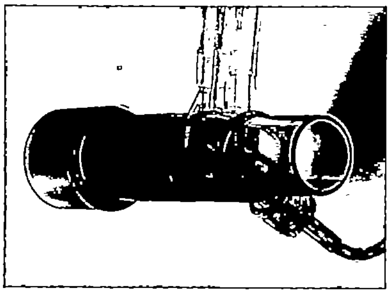

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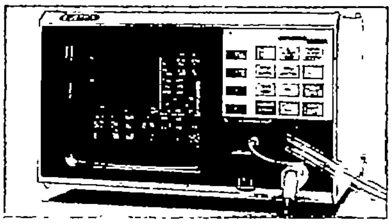

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however, persists as a dining club before the Section meetings.

The objects of the Society are the cultivation and promotion of medicine and surgery and of the branches of science connected with them, and the continued support of the Medical Library founded by the original Manchester Medical Society and presented to the Victoria University of Manchester in 1930.

The Section of Anaesthesia holds about eight meetings each year between October and May, mostly in the Manchester Medical School, but some are held at other postgraduate medical centres in the North West. The programme contains a Presidential Address, a joint meeting with the Liverpool Society of Anaesthetists and several visiting speakers from other areas. In May, in alternate years (1993, 1995, etc.), the Section invites a speaker who has made a significant contribution to anaesthesia to give the Manchester Medal Lecture. The medal and lecture are sponsored by ICI.

Membership is restricted to medically qualified people wholly or partly engaged in the practice of anaesthesia, but the meetings are open to all members of the Medical Society and to senior undergraduate and postgraduate students. Current membership totals 220.

Two prizes are competed for at the February meeting of the Section—the ICI Anaesthetic Registrars' Prize is awarded for a paper reporting research and the Abbott Prize for a paper presenting clinical material or a review of a clinical subject.

For further information contact: Mrs B. J. Lowndes, The Administrator, Manchester Medical Society, John Rylands University Library, Oxford Road, Manchester M13 9PP. Tel. 061-273 6048; Fax 061-272 8046.

MIDLAND SOCIETY OF ANAESTHETISTS

The Society was founded in 1967. Membership is open to medical practitioners engaged wholly or partly in the practice of anaesthesia and currently numbers 200.

Three regular meetings are held every year. At the Registrar's Prize Evening, held in March, papers are presented by anaesthetists-in-training. A monetary prize, currently donated by Janssen Pharmaceuticals, is awarded. This meeting may also be followed by the Biennial General Meeting of the Society. An Autumn Meeting is held to which speakers are invited to give presentations on subjects of general interest to anaesthetists (these may be non-medical). The Summer Meeting is an all-day meeting held on the second Saturday of June. A programme for guests is arranged for this meeting and the Annual Dinner of the Society takes place in the evening. The venues for the meetings are varied to take in all hospitals within the West Midlands Regional Health Authority.

Other meetings are also arranged and in recent years there has been a growing tradition of a biennial joint meeting with the Society of Anaesthetists of Wales. A Newsletter is published twice a year containing reports of the activities of the Society and presentations made to the meetings.

Further information may be obtained from: Dr B. A. C. Smith, Honorary Secretary, Midland Society of Anaesthetists, Department of Anaesthesia, City General Hospital, Stoke-on-Trent, ST4 6QG.

NORTH EAST OF SCOTLAND SOCIETY OF ANAESTHETISTS

The Society was founded in 1960 at the initiative of Dr W. N. Rollason of Aberdeen Royal Infirmary, with support from colleagues in Aberdeen and Dundee, notably the late Dr W. M. Shearer. The objects of the Society are: to disseminate knowledge and enhance the practice of anaesthesia; to form a medium for the exchange of ideas; and to promote harmony and good fellowship among members.

Four meetings are held annually—an Annual General Meeting including the Presidential Address at which registrar papers are presented and three at which guest speakers address the Society. The meetings are held at Stracathro Hospital, Brechin.

The Society consists of honorary and ordinary members. An Executive Council to manage the affairs of the Society is formed from the President, Vice-President, Past-President, Treasurer and Secretary together with four ordinary members; two from the Eastern and two from the North Eastern Region.

The Vice-President is President-Elect. Honorary membership is limited to those who have furthered the objects of the Society, or who have eminently distinguished themselves in the advancement of anaesthesia. Ordinary membership is open to all practising anaesthetists in the region which extends from Perth to Thurso.

The Society is financed largely from members' subscriptions currently at the rate of £6.00 for consultants and £3.00 for anaesthetists in training. Current membership size totals 80. Support from commercial companies is acknowledged: Glaxo provides the prize for the registrars' competition.

Further information may be obtained from: Dr C. W. Allison, Hon. Secretary, North East of Scotland Society of Anaesthetists, Strecathro Hospital, Brechin, Angus DD9 7QA. Tel. 0356-47291.

NORTH EAST THAMES SOCIETY OF ANAESTHETISTS

The Society holds two Saturday morning clinical meetings followed by lunch each year, usually in the spring at a non-teaching hospital and in the autumn at a teaching hospital. Membership is open to all anaesthetists in hospitals in the North East Thames Region holding consultant, associate specialist, staff grade or full-time clinical assistant posts.

For more details contact: Dr A. K. Mathur, Hon. Secretary, Department of Anaesthesia, North Middlesex Hospital, Edmonton, London N18 1QX. Tel 081-887 2000.

NORTH LONDON GROUP OF ANAESTHETISTS

For information on the North London Group of Anaesthetists contact: Dr J. M. Aulukh, Secretary, North London Group of Anaesthetists, West Middlesex Hospital, Isleworth, Middlesex TW7 6AF. Tel. 081-560 2121.

NORTH OF ENGLAND SOCIETY OF ANAESTHETISTS

For information on the North of England Society of Anaesthetists contact: Dr M. Stafford, Secretary, North of England Society of Anaesthetists, University Department of Anaesthesia, Royal Victoria Infirmary, Newcastle-upon-Tyne NE1 4LP. Tel. 091-222 6980.

READING ANAESTHETISTS

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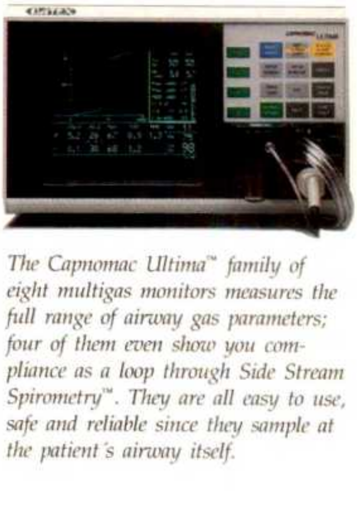

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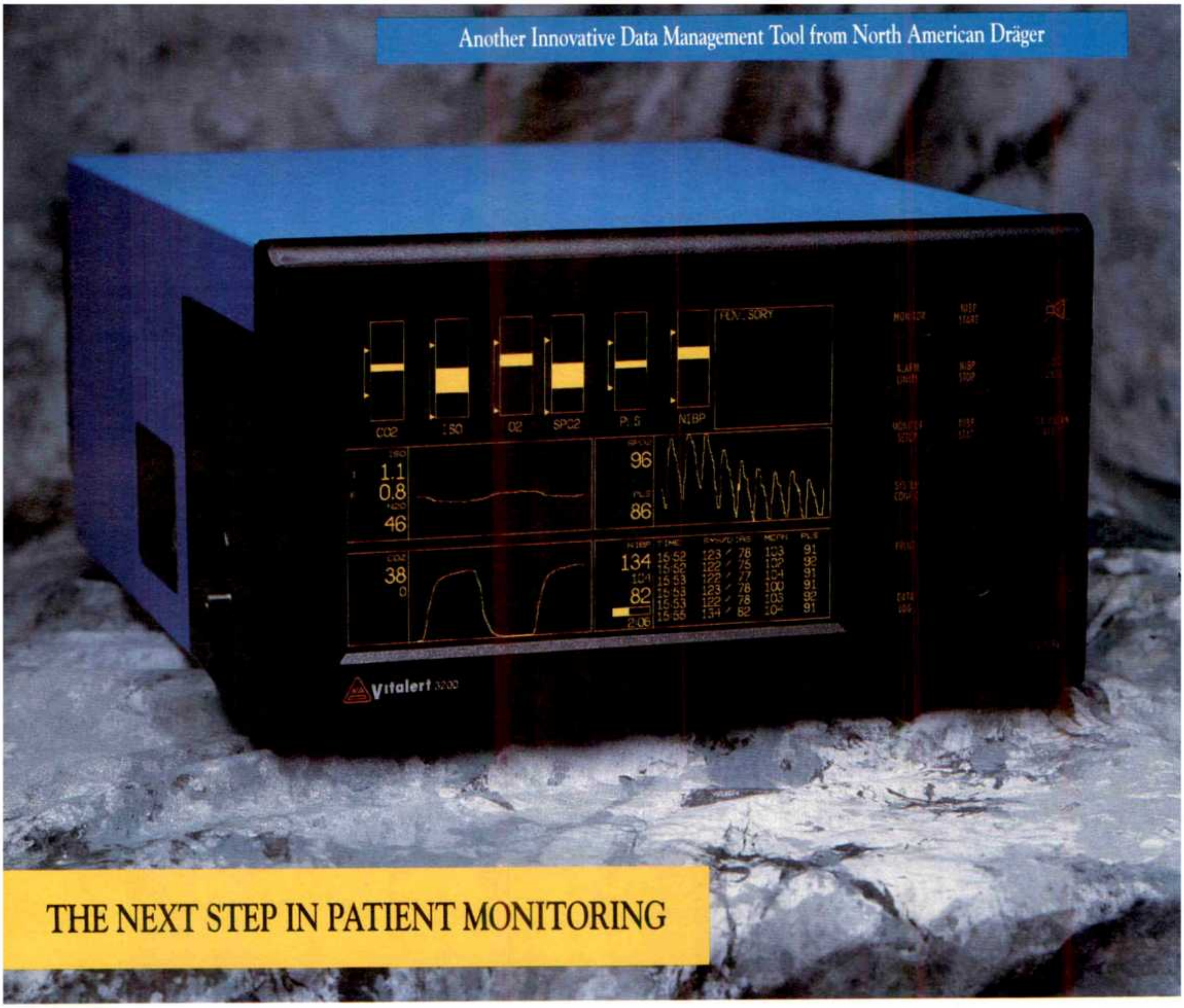
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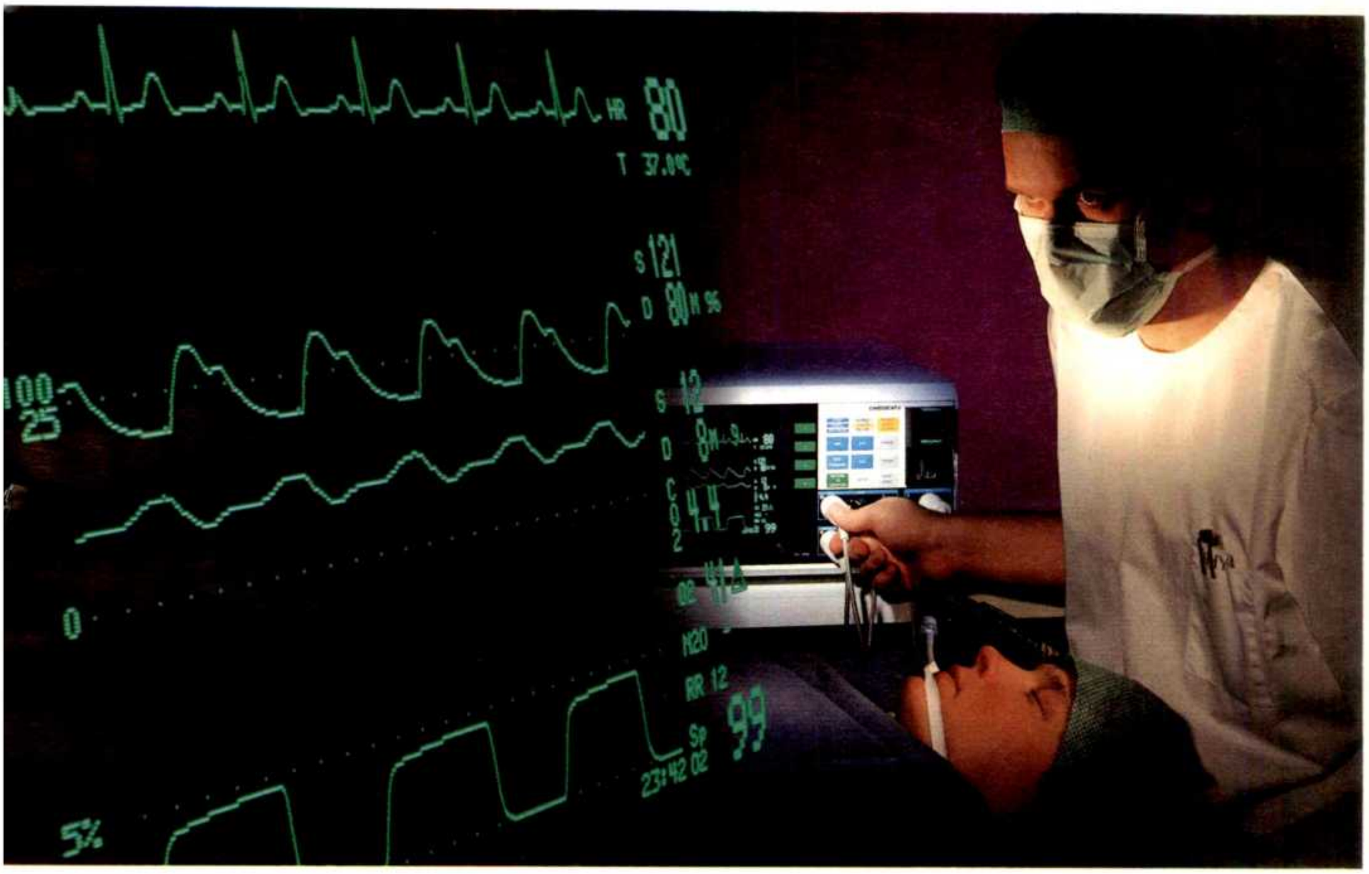

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ORIGINALIEN

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Histaminfreisetzung
bei der Einleitung von
Kombinationsnarkosen
mit Nalbuphin oder Fentanyl *

Modulierung der Reaktion durch die Prämedikation Promethazin/Pethidin

W. Dick[1], W. Lorenz[2], D. Heintz[1], H. Sitter[2] und A. Doenicke[3]
[1] Klinik für Anästhesiologie, Johannes Gutenberg-Universität Mainz
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[3] Institut für Anästhesiologie, Ludwig-Maximilians-Universität München

Zusammenfassung

In einer kontrollierten klinischen Studie an 24 allgemeinchirurgischen Patienten wurde die Histaminkonzentration während der Einleitungsphase einer Kombinationsnarkose mit Nalbuphin (1 mg/kg) oder Fentanyl (5 µg/kg) untersucht. Zur Prämedikation erhielten die Patienten Promethazin (Atosil®) und Pethidin (Dolantin®) 30 min vor den Opioiden. Die Narkoseeinleitung erfolgte mit Alcuronium-Flunitrazepam-Thiopental-Succinylcholin. Nach der Intubation wurde die Analgesie mit Nalbuphin oder Fentanyl aufrechterhalten. Nalbuphin und Fentanyl erwiesen sich als Histaminfreisetzer mit einer mehr als 40%igen Inzidenz. Nalbuphin aber modulierte (potenzierte) noch dazu die Histaminfreisetzung durch die Kombination Alcuronium-Flunitrazepam-Thiopental. Dieser Unterschied zwischen Nalbuphin und Fentanyl war statistisch signifikant (Inzidenz 46% gegen 9%!). Eine direkte Korrelation zwischen Histaminfreisetzung und hämodynamischer Instabilität konnte nicht nachgewiesen werden. Auch eine detaillierte Kausalitätsanalyse mit bedingten Wahrscheinlichkeiten und der Annahme einer beitragenden Determinante für Histamin ergab, daß die Histaminfreisetzung die gemessenen hämodynamischen Parameter kaum beeinträchtigt. Eine mögliche Ursache dieser Ergebnisse besteht in der zeitgerechten vorherigen Gabe von Promethazin, das sowohl eine starke H_1-antagonistische Wirkung wie auch eine H_2-antagonistische Wirkung entfaltet.

Schlüsselwörter

Histamin · Randomisierte Studie · Nalbuphin · Fentanyl · Antihistaminika

Histamine release during induction of anaesthesia with nalbuphine or fentanyl. Modulation of the reaction by premedication with promethazine/pethidine

Abstract

In a controlled clinical trial in patients admitted for general surgery (mainly abdominal and thyroid), histamine release following nalbuphine 1 mg/kg i.v. versus fentanyl 5 µg/kg i.v. was studied in the course of an otherwise routine induction with promethazine/pethidine as premedication 30 min before the opioids and alcuronium - flunitrazepam - thiopental 5 min later. Succinylcholine was given before intubation and further analgesia was obtained by repeated administration of either nalbuphine or fentanyl. Plasma histamine levels were measured by a specific fluorometric assay, heart rate and blood pressure were measured for assessing hemodynamics, and clinical signs of anaphylactoid reactions such as skin eruptions and arrhythmias were registered.

Results. Nalbuphine and fentanyl both released histamine with an incidence of more than 40%. In addition, nalbuphine potentiated the histamine release evoked by the sequential administration of alcuronium-flunitrazepam-thiopental in one complex of application. The incidence of histamine release in the nalbuphine group was 6/13 = 46%, in the fentanyl group only 1/11 = 9% (chi² test, $P < 0.05$). Furthermore, this study showed high histamine levels after succinylcholine and intubation in a relation to time of administration that suggested histamine release as a stress response to intubation. Finally, the incidence of histamine release after a second injection of the opioids was still 30%. A direct correlation between plasma histamine levels, hemodynamic changes, and skin reactions could not be shown. A detailed causality analysis with histamine release as a contributory determinant showed histamine release less detrimental to hemodynamic stability than the opposite, which had been expected. However, the promethazine administered 30 min before induction of anaesthesia had strong H_1- and H_2-receptor antagonistic activity and was given with optimum timing for H_1- and H_2-prophylaxis.

Conclusion. The study demonstrated that histamine release during anaesthesia and surgery depends strongly on the time sequence of drugs and measures

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Further information may be obtained from : Dr Chandy Verghese, College Tutor, Department of Anaesthetics, Royal Berkshire Hospital, London Road, Reading RG1 5AN. Tel. 0734-877065.

SHEFFIELD AND EAST MIDLANDS SOCIETY OF ANAESTHETISTS

The Society was formed in 1946 as the Sheffield Society of Anaesthetists. At the inception of the NHS in 1948 the title was changed to Sheffield and East Midlands Society of Anaesthetists and membership opened to all practising anaesthetists in what was then the area covered by the Sheffield Regional Hospital Board. At present the Society has well over 250 members from the Trent Region, South Yorkshire, Lincolnshire and Peterborough. Membership is open to all medical practitioners engaged in the practice of anaesthesia and allied specialties, in the Trent Region and South Humberside.

The objects of the Society are to promote the study and development of anaesthesia and scientific meetings are held three times a year in March, May and September. The May meeting is combined with the Annual General Meeting and is held in the district of the incoming president. The Autumn meeting is now an all day meeting with the annual dinner to follow. All trainees are encouraged to attend. The evening meetings are held on weekdays with a buffet supper preceding. The Society offers two annual prizes to a registrar and an undergraduate for essays in a wide choice of subjects preferably with some reference to the specialty. The shortlisted entrants are expected to present the essays at the autumn meeting and the winner is picked on the day.

The Society is managed by the Council comprising the President, Vice-President, Treasurer, Joint Secretaries and representatives from the different areas. Nominated members may also be accepted from outside the areas mentioned.

For further information contact the Joint Secretaries: Dr P. N. Reed, Peterborough District Hospital, Peterborough PE3 6DA. Tel. 0733-67451 or Dr P. J. Mathews, Rotherham District Hospital, Moorgate Road, Rotherham S60 2UD. Tel. 0709-820000 (ext. 5550).

SOCIETY OF ANAESTHETISTS OF THE SOUTH WESTERN REGION

The Society was formed at an inaugural meeting in Bristol in 1947 with the object of promoting the art and knowledge of anaesthesia. Initially meetings were held three times a year, occupying both Friday and Saturday, but for over 30 years only two meetings have been held each year. The Annual General Meeting is held in Bristol in November of each year although every fourth year this meeting is held in Bath. The spring meeting is generally held in one of the hospital districts in the Region although some very successful meetings have been held elsewhere in the U.K., such as Oxford, Cambridge and Southampton. Every third year the spring meeting is held abroad in conjunction with a local Society. Visits so far have been made to Bruges, Amsterdam, Berlin, Copenhagen, Oporto and Strasbourg. Emphasis has been laid not only on the academic content of the meetings, but also on the promotion of friendship and conviviality between the members themselves and those of other Societies.

Management of the Society is in the hands of its President, Officers and a committee which includes a junior staff representative. Membership is open to any anaesthetist or members of allied professional occupations with a special interest in anaesthesia. Honorary members have included Dr E. G. Bradbeer, Dr G. L. Feneley, both founding members, Professor T. C. Gray, Professor Sir Robert Mackintosh, Sir Ivan Magill, Professor Sir Geoffrey Organe and Professor J. Clutton-Brock.

The journal, *Anaesthesia Points West*, was inaugurated in 1968 and publishes scientific articles, Society news, and other items of interest both general and specialized. It is published twice-yearly and is under the control of an Editor, Assistant Editor and Editorial Board. Prizes are awarded annually to suitable entrants who have contributed to anaesthetic knowledge in the region at junior staff level. The Registrar's prize is based on an essay on a topic of the entrant's own choice with the winner being encouraged to read the paper at the Annual General Meeting in the autumn. The President may also award his own discretionary prize to another candidate or to any member of the junior staff in the region whom he considers to have contributed in some special way to the advancement of the speciality.

The lively interest provoked by the topics discussed at the meetings as well as the pleasant aspects of the social participation in the various programmes is reflected in the growth of the membership which totals about 500 members.

Further information on the Society's functions and membership may be obtained from: Dr Leslie E. Shutt, Hon. Secretary, Department of Anaesthetics, St Michael's Hospital, Southwell Street, Bristol BS2 8EG. Tel. 0272-285203; Fax 0272-291498.

SOCIETY OF ANAESTHETISTS OF WALES

The Society was founded in 1948 and was originally called the Society of Anaesthetists of South Wales. The aims of the Society are to advance the knowledge and practice of anaesthesia, to encourage the exchange of ideas and further harmony and friendship amongst anaesthetists.

Membership of the Society is open to registered medical practitioners wholly or partly in the practice of anaesthesia. Junior anaesthetists working in Wales are members as of right and there is no annual subscription for junior membership. Retiring members of the Society are automatically granted honorary membership. The annual subscription is £10.

The affairs of the Society are administered by a council chaired by its President. Members of the Council include the officers of the Society and four ordinary members. The Council is elected by the members at the Annual General Meeting and the constitution states that, as far as possible, membership of the Council should be representative of all parts of Wales.

The Society holds three meetings a year, a Spring Scientific Meeting, a Summer Clinical Meeting and an Autumn Dinner. The Spring Scientific Meeting is a one day meeting held in March where prizes for presentations by anaesthetists in training are awarded. The Summer Clinical Meeting is a weekend meeting held in June and is concluded by the Annual General Meeting. This meeting is sometimes held in conjunction with other Societies and is often held outside Wales. The Autumn Dinner is held in November and is currently preceded by a short clinical meeting.

The pharmaceutical and medical equipment industries lend financial support to the Society's clinical meetings and this is acknowledged gratefully.

For further information contact: Dr Graham J. Arthurs, Hon. Secretary, Department of Anaesthetics, Wrexham Maelor Hospital, Croesnewydd Road, Wrexham, Clwyd, North Wales LL13 7TD. Tel. 0978-291100 (ext. 5955/6).

SOUTH EAST THAMES SOCIETY OF ANAESTHETISTS

This Society evolved in the late 1950s from the South London Anaesthetic Society. It was renamed the South East Metropolitan Regional Anaesthetic Society and included all the hospitals in the South East Metropolitan Region. On the reorganization of the Health Service the name was changed to the South East Thames Society of Anaesthetists.

This Society holds two meetings a year, the winter meeting in London and the summer meeting in the periphery. The meetings consist of papers and discussion and sometimes visits to new hospitals or departments. On occasion, the visits may be to non-medical centres. Combined meetings have been held both at home with other British Societies and with Dutch, Danish, French and German Societies, at home and abroad.

Membership is open to all anaesthetists of consultant grade in the South East Thames Region. Junior staff are encouraged to attend as guests of the members. There is no membership subscription, members are required only to pay the cost of meetings.

For further information please contact: Dr John Wedley, Hon. Secretary, St Thomas' Hospital, Lambeth Palace Road, London SE1 9RT. Tel. 071-928 9292.

SOUTHERN SOCIETY OF ANAESTHETISTS

The Society was founded in 1948 consisting of anaesthetists from the South West Metropolitan and Wessex Regions together with many teaching and postgraduate hospitals in and around London. It is open to all anaesthetists (senior, junior, or retired) who work or have worked in the area.

The first President was Dr Ivan Magill. The current President is Dr Andrew Doughty.

Meetings are held three times a year: the winter meeting is usually hosted by a teaching or specialist hospital. The Society arranges the summer meeting to be in the country or by the sea!

For further information contact: Dr Jeremy Cashman, Hon. Secretary, Department of Anaesthetics, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel. 081-672 1255.

YORKSHIRE SOCIETY OF ANAESTHETISTS

The Yorkshire Society of Anaesthetists was founded at an inaugural meeting held in Leeds General Infirmary in November 1947 with an initial membership of approximately 30. The aims, aspirations and rules of the Society were drawn up at this meeting and although there have been detailed revisions since then there has been no reason to make any fundamental alterations. The aims of the Society are to promote friendship, mutual help and scientific advancement in the speciality, and to make recommendations, when necessary, for the furtherance of the work of anaesthetists. All medically qualified practitioners interested in anaesthesia are eligible for full membership, and may be elected at a general or ordinary meeting on being proposed and seconded by two members. Trainee anaesthetists, members of other anaesthetic societies and other persons with an interest in anaesthesia are eligible for associate membership. Honorary membership may be conferred by the Society on the recommendation of the committee.

The affairs of the Society are administered by an Executive Committee consisting of a President, Vice-President, Secretary, Treasurer and six other members. The President holds office for two years. The office of Vice-President is held alternately by the retiring President and the President-Elect for one year each.

Meetings are held monthly from September until May. The Annual General Meeting is held in February in the Littlewood Hall, Leeds General Infirmary. There is an all day meeting at one of the regional hospitals in March and informal social meetings are also held. The Registrar's prize is competed for at the May meeting of the Society and a prize is awarded for a paper reporting research or presenting a clinical subject.

Further information can be obtained from: Dr M. Boylan, Department of Anaesthesia, General Infirmary, Great George Street, Leeds LS1 3EX. Tel. 0532-437172 (direct line).

University Departments of Anaesthesia

BELFAST

The University Department of Anaesthetics in Northern Ireland, founded in 1957, is attached to the Queen's University of Belfast and is situated in the Whitla Medical Building at 97 Lisburn Road, close to the University and the Belfast City Hospital. Its staff work at most of the teaching hospitals in Belfast and at the Craigavon Area Hospital.

The medical staff consists of a professor, two senior lecturers, one part-time and honorary lecturer and five senior tutors/tutors (lecturers). All are employed jointly by the University and Department of Health and Social Services and divide their time between clinical and academic work. There is also a variable number of research fellows, financed from outside funds, carrying out research for the degree of Ph.D. or M.D.

The University Department in conjunction with the Northern Ireland Council for Postgraduate Medical Education is responsible for the teaching and training of anaesthetists throughout Northern Ireland. There are courses directed towards all three parts of the F.R.C.Anaes. and F.F.A.R.C.S.I. examinations. For those new to the specialty, there is a six-week introductory course in August and September dealing mainly with clinical aspects. The teaching is held throughout the Michaelmas and Hilary terms two afternoons a week or in modules, but whole-time revision courses are also held before the main examinations.

Undergraduate teaching is arranged by the University Department and practical classes, tutorials and lectures take place during the first, second, third and fourth years. The emphasis of this teaching is on clinical pharmacology, resuscitation and the wider role of the anaesthetist in intensive and postoperative care.

RESEARCH

Research in the Department of Anaesthetics has always been concerned mainly with clinical pharmacology, particularly of new drugs, but this involves usually a thorough reassessment of older drugs. The main fields of interest at present are i.v. anaesthetics (including the benzodiazepines), inhalation anaesthetics, premedicants, anticholinergics and analgesics. Measurement of plasma concentrations by gas-liquid and high performance liquid chromatography enables a better evaluation of the pharmacokinetics of new drugs. The University has also had a strong involvement in research on neuromuscular blocking drugs and this is continuing with the constant advent of new drugs. Other clinical fields of research have included studies with clonidine, and regional analgesia generally.

For further information contact:

Professor R. S. J. Clarke,
Department of Anaesthetics,
The Queen's University of Belfast,
Whitla Medical Building,
97 Lisburn Road,
Belfast BT9 7BL.
Tel. 0232-245133 (ext. 2208).
Fax 0232-329605.

BIRMINGHAM

The Featherstone Department of Anaesthesia and Intensive Care at the University of Birmingham, is based at the Queen Elizabeth Hospital adjacent to the main University campus with a suite of offices and research laboratories in the Clinical Research Block as well as offices in the main hospital building. The Department has extensive assay and near-patient monitoring facilities.

The medical staff comprises a professor, three senior lecturers (anaesthesia, anaesthesia and intensive care, and paediatric anaesthesia) and three lecturers. In addition, it holds the five-year Senior Lectureship in Intensive Care donated jointly by the Association of Anaesthetists and the Royal College of Anaesthetists and has a regular complement of research fellows funded from external monies and overseas attachments. The medical staff hold honorary contracts with the West Midlands Regional Health Authority and undertake clinical sessions in anaesthesia and intensive care.

The Department is responsible for the teaching of resuscitation and aspects of perioperative care to medical and dental students and has medical student attachments in intensive care. All members of the Department contribute to postgraduate teaching for the three parts of the F.R.C.Anaes. examination at local and national courses and play a major role in the locally organized residential courses for parts 1 and 2.

RESEARCH

The Department undertakes research in five main areas of interest as well as supporting a wide range of smaller projects undertaken by junior staff in training, the majority of the lecturers and research fellows undertaking research work submit a thesis for the degrees of M.D. or M.Med.Sci.

(1) Intensive care—changes in gut permeability, continuous i.v. sedation, induced nitric oxide synthase in sepsis syndrome and continuous intra-arterial monitoring and sedation.
(2) Paediatric anaesthesia—non-invasive respiratory monitoring, neonatal ventilatory monitoring and sedation.
(3) Cardiac anaesthesia—sedation and analgesia, post-bypass hypertension, temperature control, acute lung injury and measurement of arterial pressure.
(4) Clinical measurement—drug delivery systems, non-invasive blood pressure measurement, capnometry analysis and the development of expert decision support systems in anaesthesia.
(5) Day-case anaesthesia—use of short-acting drugs, recovery and optimal technique.

For further information contact:

Professor P. Hutton,
Featherstone Department of Anaesthesia and
Intensive Care,
University of Birmingham,
Queen Elizabeth Hospital,
Edgbaston,
Birmingham B15 2TH.
Tel. 021-627 2060. Fax 021-627 2062.

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Department of Anaesthetics,
The Queen's University of Belfast,
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Belfast BT9 7BL.
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clinic, block therapy sessions and the obstetric anaesthesia and analgesia service. All consultants hold honorary contracts in the Clinical Research Centre.

A clinical meeting is held every Monday at 17:00. Grand rounds are held daily in the ITU at noon. In addition, weekly tutorials and organized teaching sessions are arranged in connection with the various examinations.

The staff of the NHS Directorate currently consists of: nine consultants, three senior registrars, five registrars, and five senior house officers. In addition, a newly appointed senior lecturer (affiliated to the St Mary's Professorial Unit with consultant status) administers audit and teaching in the Directorate as well as research in the new NHS Directorate Anaesthetic Research Unit.

RESEARCH

The MRC currently continues to support an Anaesthesia and Hyperbaric Research Group at the Clinical Research Centre. In addition the NHS is building up a new Anaesthetic Research Unit at Northwick Park Hospital as described above. The research interests of their groups of investigators include molecular mechanisms of anaesthesia, auditory and spinal evoked responses, metabolic studies, ITU sedation trials, pressure reversal of anaesthesia and a variety of additional topics related to the interests of individual senior staff.

For further information contact:
Northwick Park Hospital, Directorate of Anaesthesia:
Dr A. M. Hewlett (Clinical Director)
Northwick Park Hospital,
Watford Road,
Harrow, Middlesex HA1 3UJ.
Tel. 081-869 3969.
Fax 081-869 3975.
Clinical Research Centre Division of Anaesthesia:
Dr M. J. Halsey (Head of Anaesthesia HPNS Research Group)
Clinical Research Centre,
Watford Road,
Harrow, Middlesex HA1 3UJ.
Tel. 081-869 3401.
Fax 081-423 1275.

EDINBURGH

The University Department of Anaesthetics is based in the Royal Infirmary and the Western General Hospital, Edinburgh, and works alongside the Clinical Division of Anaesthesia that is responsible for anaesthetic and related services throughout the Lothian Region.

Teaching (lectures and clinical demonstration) is given to undergraduate medical and dental students. Medical students are attached to the Department for one week with an opportunity to extend this period by a further week. In addition, students from this or other universities may spend a 4–8 week elective period in the Department.

The Department organizes in-service teaching for senior house officers preparing for the Part 1 F.R.C.Anaes. examination and, in conjunction with the Postgraduate Board for Medicine, courses for those preparing for the Parts 2 and 3 F.R.C.Anaes. examinations. In addition, the Department holds twice-yearly, one week, open courses, Basic Concepts in Anaesthesia and Scientific Basis of Anaesthesia and an annual two-day course in local anaesthesia. There are clinical attachments for postgraduates from overseas.

RESEARCH

The Department has a wide range of research interests in the fields of:

1. Inhalation anaesthesia—effects of trace concentrations of anaesthetic agents on performance and health; anaesthetic breathing systems; applications of mass spectrometry; toxicology of inhalation anaesthetic agents.
2. Respiratory physiology—effects of anaesthesia on respiratory function in the perioperative period; application of non-invasive techniques in the measurement of respiratory movement.
3. Postoperative pain relief—local anaesthetic techniques; specific uses of non-steroidal anti-inflammatory and opiate drugs.
4. Local anaesthesia—*in vitro* testing of local anaesthetic agents; profiles of individual drugs.
5. Intensive care—oxygen transport during critical illness; sedation techniques.
6. Neuroanaesthesia and neurosurgical intensive care.

For further information contact:
Professor A. A. Spence,
Department of Anaesthetics,
Royal Infirmary,
Edinburgh EH3 9YW.
Tel. 031-229 2727 (direct).
Fax 031-229 3337.

GLASGOW

The Department of Anaesthesia associated with the University of Glasgow has accommodation and laboratory space in both the Royal Infirmary and the Western Infirmary. Although primarily responsible for their own "parishes" the two components of the Department liaise to arrange, with the West of Scotland Committee for Postgraduate Medical Education, a day-release course of lectures and practical demonstrations on the Scientific Basis of Anaesthesia for those candidates preparing for the Parts 1 and 2 of the F.R.C.Anaes. diploma, and concentrated courses of one-week's duration before each diet of the Part 3. Regular tutorials are given throughout the year in each centre and specialist courses on current topics in anaesthesia are arranged. Clinical attachments for overseas postgraduates can be arranged and a taught course leading to the degree of M.Sc. in anaesthesia is available to suitably qualified applicants.

Contributions are made to the undergraduate teaching programme on the clinical pharmacology of anaesthetic drugs, the management of acute respiratory failure and on techniques and apparatus used in respiratory intensive care. Teaching in anaesthesia includes clinical instruction in the pre- and postoperative management of patients, visits to operating theatres and practical instruction in resuscitation and inhalation therapy.

Undergraduate studentships of approximately 4–6 weeks' duration are available for students from this and other universities wishing to undertake a period of elective study in anaesthesia and/or intensive care.

RESEARCH

Pathophysiology and management of pulmonary injury in burned patients; computer applications in medical education, anaesthesia, intensive care and artificial intelligence; physiology and anaesthetic pharmacology in relation to the cerebral circulation and the hepatic circulation. Studies in the management of acute pain: assessment of new agents and methods of drug delivery.

Closed-loop automatic control of anaesthesia and neuromuscular block. Closed loop control and modulation of arterial pressure. Explicit and implicit memory in association with anaesthesia. Machine intelligence in the control of general anaesthesia. Postoperative epidemiological audit.

In the pursuit of its research interests, the Department has forged close links with other departments in this and other universities. For example: Behavioural Sciences, Bioengineering (Strathclyde), Computer Sciences, Control Engineering (Sheffield), Exercise and Sports Medicine, Mechanical Engineering, Microbiology, Neuropathology, Neurosurgery, Public Health.

For further information contact:
Professor William Fitch,
University Department of Anaesthesia,
Glasgow Royal Infirmary,
8–12 Alexandra Parade,
Glasgow G31 2ER.
Tel. 041-552 3535 (ext. 5448).
Fax 041-552 3229.

LEEDS

The Chair of Anaesthesia in Leeds was established in 1964. The current Academic Unit is situated in both the General Infirmary and St James's University Hospital (the main department is at St James's). The full-time academic staff include a professor, two senior lecturers and three lecturers.

The undergraduate course in anaesthesia is held in both hospitals and other selected hospitals within a 20-mile radius of Leeds and lasts for three weeks. The students attend a structured course of tutorials and clinical instruction for the first two weeks and in the third week each is attached to one consultant anaesthetist. Students have an option to study for a B.Sc. in a joint programme between the Academic Unit of anaesthesia and other departments, including basic science departments. Anaesthetists contribute to topic teaching sessions on an *ad hoc* basis.

The Unit runs courses suitable for F.R.C.Anaes. candidates. The postgraduate course related to the Part 2 is held biannually, and the Part 3 course is on a fortnightly day-release basis for anaesthetic trainees in the Yorkshire Region.

RESEARCH

The Unit is very active in research into the abnormalities of muscle metabolism associated with malignant hyperthermia and other related syndromes, and other muscle diseases, and into the neuropharmacology of sensory transmission in the spinal cord, with particular emphasis on the benzodiazepine receptor and analgesia. There is involvement in the psychological aspects of patients with chronic pain. The Unit has an interest in dental anaesthesia and sedation.

The Academic Unit has extensive instrumentation for measurement of pressures, flows, radioactivity, gas concentrations with respiratory mass spectrometry, high performance liquid chromatography, spectrophotometry and measurement of intracellular calcium ion concentration and enzyme activity.

The Unit offers a national service for screening patients and their families for malignant hyperthermia. Staff of the Unit maintain a hotline service (see below for details) and a computerized national registry.

Members of the Unit have regular commitments to the Pain Management Services in both teaching hospitals.

For further information contact:
Professor F. R. Ellis,
Academic Unit of Anaesthesia,
Department of Clinical Medicine,
Clinical Sciences Building,
St James's University Hospital,
Leeds LS9 7TF.
Tel. 0532-433144 (ext. 5274).
Fax 0532-836972.
Hotline Tel. 0345-333111 (bleep 0525 420).

LEICESTER

The University Department of Anaesthesia in the University of Leicester was founded in 1979, one year before the first students graduated from the School of Medicine. The Department was based initially at Leicester General Hospital, but in 1983 some two-thirds of the Department moved to join with the NHS Division of Anaesthesia in new premises at the Leicester Royal Infirmary site. Currently, the Department comprises a professor and head of department, three senior lecturers, three lecturer/senior registrars, four lecturer/registrars, four research fellows, one honorary clinical lecturer, five technicians and two research sisters. In addition, considerable technical assistance is provided by the Medical Physics Department at Leicester Royal Infirmary. In 1992, a non-clinical lecturer in pharmacology was appointed, together with a postdoctoral research fellow, and additional laboratory accommodation obtained.

The University Department liaises closely with the Division of Anaesthesia to provide formal lecture courses for the F.R.C.Anaes. Parts 1, 2 and 3 examinations. In addition, formal lectures are given in the undergraduate course during full-time two-week secondments to anaesthesia during the fifth year and on a regular but less frequent basis during the third and fifth years in pharmacology and surgery, respectively. Facilities are available for students who wish to take an elective period of study in anaesthesia.

Formal postgraduate training comprises a one-week whole-time course for Parts 1, 2 and 3 F.R.C.Anaes. in January, October and May, respectively, and a half-day release revision course for Part 3 F.R.C.Anaes. in November. Lunch-time seminars are organized by the University Department at Leicester General Hospital, Leicester Royal Infirmary and Glenfield General Hospital. There is also a Journal Club. The University Department also organizes monthly guest lectures and research meetings. In collaboration with the Division of Anaesthesia, regular meetings are held every Wednesday in the form of invited lectures, morbidity and mortality conferences and combined surgical and anaesthetic case conferences.

Currently the Department provides accommodation and secretarial assistance for the Editor of the *British Journal of Anaesthesia*, supported by associate and assistant editors.

RESEARCH

Laboratory facilities include a biochemistry laboratory, a tissue culture laboratory and a medical physics laboratory at LRI, and medical physics and sleep laboratories at Leicester General Hospital. Collaborative research activities with the Department of Medicine provide access to facilities in the Clinical Sciences Building. Current research activities include:

(1) Studies of postoperative analgesia utilizing self-administration systems and non-parenteral methods of systems of analgesic drugs.

(2) Pharmacokinetic studies of analgesic and non-analgesic drugs of anaesthetic interest.
(3) The development of inductance plethysmography for assessment of respiratory changes in the post-operative period and for studies of sleep apnoea and cot-death syndromes.
(4) Investigations of activities of opioid receptors to analgesic and other agents.
(5) Clinical investigations of the effects of drugs in the perioperative period.
(6) Studies of the mechanisms of actions of anaesthetic and analgesic drugs involving *in vitro* neural preparations at both cellular and subcellular levels.

For further information contact:
Professor G. Smith,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Tel. 0533-585291 (Direct line).
Fax 0533-854487.

LIVERPOOL

The University Department is situated in the University Clinical Departments building of the Royal Liverpool University Hospital. Although it is run as a separate entity from the National Health Service Anaesthetic Department in the same hospital, there are many areas of common involvement.

The Department consists of a professor, four senior lecturers and two lecturers. A senior registrar is attached usually to the Department under the supervision of the academic staff. The Professor of veterinary anaesthesia and his colleagues are members of the department.

Lectures are given to second year, fourth year and final year undergraduate students. During the final year, tutorials are also given to students attached to hospitals in the region to gain practical instruction.

The postgraduate course is intended to cover material for the F.R.C.Anaes. examination and has now been divided into Part 1, Part 2 and Part 3. It involves a half-day release during autumn and lent terms. Tutorials are held within the University Department of Anaesthesia and in postgraduate teaching centres.

Positions on the Part 1 course are associated with SHO posts in anaesthesia and a limited number of supernumerary students can be accepted.

Practical experience is combined with tutorials and lectures in the University Department of Anaesthesia, Royal Liverpool University Hospital, both from the teaching hospital staff and from lecturers invited from other parts of the country.

Registrar and senior registrar training rotations are provided within the Mersey region to enable junior anaesthetic staff to gain practical training in all the specialities. The Department plays an active role in medical audit.

RESEARCH

A wide variety of research activities are pursued within the Department. New muscle relaxants, their effects and pharmakokinetics have been widely studied and new pharmacodynamic models developed. Volatile anaesthetics have formed the basis of a continuing research investigation, together with methods of gas analysis and patient monitoring. Principles of safety of anaesthetic equipment are both taught and researched, reflecting an interest in the design of anaesthetic equipment. The effects of anaesthesia on implicit memory formation are under investigation.

There is an active participation in research associated with the Magnetic Resonance Research Centre including the development of fibre-optic monitoring. Research facilities are also provided in intensive therapy and for studies into pain relief.

For further information contact:
Professor J. E. Utting,
University Department of Anaesthesia,
Royal Liverpool University Hospital,
P.O. Box 147,
Liverpool L69 3BX.
Tel. 051-706 4001.
Fax 051-706 5815.

LONDON: CHARING CROSS AND WESTMINSTER MEDICAL SCHOOL

The Academic Department of Anaesthetics at present is based in the Magill Department at Westminster Hospital, where the first chair in anaesthesia at London undergraduate hospital was established. The department is fully integrated with the NHS staff at Charing Cross Hospital and Westminster Hospital. Members of the department have clinical responsibilities and the NHS consultant and junior staff have open access to research facilities and participate actively in clinical and basic scientific research as well as postgraduate and undergraduate teaching. There is a major commitment to postgraduate education on both sites. Regular weekly teaching sessions occur at both Charing Cross (Wednesday afternoon) and Westminster Hospitals (Thursday evening and one Wednesday afternoon a month). A half-day annual Magill International Symposium and a Riverside Intensive Care meeting is held in the winter term at Westminster. Internal courses for Part 1 and Part 3 for the F.R.C.Anaes. examination take place on both sites and the Department participates in Part 2 courses organized by other bodies.

RESEARCH

The department has a large research output. At Charing Cross Hospital, the main work is on local anaesthetics, pain and intensive care. Facilities exist on this site for large animal work. At Westminster there is a major ongoing programme on the pharmacology of neuromuscular transmission, neuromuscular blocking drugs and pharmacodynamics. Other research interests include the performance of anaesthetic equipment and anaesthetic circuits, respiratory function and central neurotransmitters. A large active intensive care unit on both sites is under the direction of members of the academic staff and provides material for clinical research and teaching. There is a dedicated research post (SIMS Fellow) available for research leading to an M.D. in the Magill Department.

For further information contact:
Professor Stanley Feldman,
Magill Department of Anaesthetics,
Westminster and Chelsea Hospital,
Fulham Road,
Chelsea,
London SW10 9TH.
Tel. 081-746 8025/8024.
Fax 081-746 8801.

LONDON: INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET

The Portex Department of Paediatric Anaesthesia was established in April 1991 following a generous donation to the University of London by Smiths Industries. The Department consists of a professor, non-clinical senior lecturer (respiratory physiology), clinical lecturer and research fellow. Following reorganisation within the Institute of Child Health, the Department has become an integral part of the larger Unit of Anaesthesia, Intensive Therapy and Respiratory Medicine, itself within a newly formed Division of Physiology and Pharmacology. The academic unit has within its space the NHS Pulmonary Function Laboratory and there are close links with the NHS Anaesthetic Department. Members of the academic and clinical departments are heavily involved in postgraduate teaching of paediatric anaesthesia at local, national and international level. Joint weekly meetings are held together with journal clubs in anaesthesia and respiratory medicine.

RESEARCH

The academic unit's research laboratories are housed on the University floor of the cardiac wing of the Hospital. One of the main research themes is the study of the effects of anaesthesia and intensive therapy on lung function in infants and young children. Three members of the Unit are currently registered as Ph.D. students. In collaboration with the Vascular Biology Unit, a new research laboratory has been established to study the physiological and pharmacological responses of the developing pulmonary vasculature and airways. Research links in this field have been established with the Mayo Clinic (U.S.A.) and with the Karolinska Institute in Stockholm.

The research plans of the University and Hospital departments have been fully integrated, all new protocols being peer reviewed by members of both departments.

For further information contact:

Professor D. J. Hatch,
Portex Department of Paediatric Anaesthesia,
Institute of Child Health,
30 Guilford Street,
London WC1N 1EH.
Tel. 071-242 9789 (ext. 2382).
Fax 071-829 8634.

LONDON: KING'S COLLEGE SCHOOL OF MEDICINE AND DENTISTRY

The Academic Department of Anaesthesia was set up in the mid-1960s and is staffed by two senior lecturers and one secretary. In addition, there are variable numbers of research registrars and research nurses on short-term appointments, funded by charities (one at present).

The Department runs a three-week teaching programme for the School's medical undergraduates comprising twice-weekly tutorials, theatre work, intensive therapy unit (ITU) experience and attendance at the Chronic Pain Relief Clinic. Dental undergraduates are taught once a week.

Postgraduate teaching for junior members of the hospital staff is run also by the Department in the form of group and individual tutorials for fellowship examinations. Dental postgraduates are regularly taught on the subjects of analgesia, sedation and prescription of i.v. fluids. In addition, teaching for theatre/ITU nurses, midwives and physiotherapists is also provided.

The clinical staff of the Department provide service cover for the following surgery (number of weekly sessions): cardiothoracic (4), obstetric (3), in addition to two chronic pain relief sessions.

RESEARCH

The research interests of the members of the Department, including collaboration with other departments, cover the following areas: metabolic effects of bronchodilators; pharmacokinetics of analgesic agents and ventilatory effects of analgesics.

For further information contact:

Dr J. Ponte,
King's College Hospital,
Denmark Hill,
London SE5 9RS.
Tel. 071-326 3358.

LONDON: LONDON HOSPITAL MEDICAL COLLEGE

The Research Department of Anaesthetics at the Royal College of Surgeons founded in 1957 and the Anaesthetics Unit at the London Hospital Medical College established in 1967 are amalgamated as the Anaesthetics Unit.

The staff consists of the BOC Professor of Anaesthesia, seven senior lecturers and four lecturers. In addition, there is technical and research nursing support. The Royal London Hospital and Newham General Hospital provide the main clinical base with emphasis on service for other academic units. Senior registrars are seconded to the Anaesthetics Unit, for 6-month periods, from the senior registrar rotational scheme based at the Royal London Hospital.

Teaching of both undergraduates and postgraduates is carried out. Medical undergraduates can undertake a two-week programme and there is also extensive teaching for dental undergraduates. There is a monthly audit meeting and then evening visiting lecturers during academic term time.

RESEARCH

The research interests of the members of the Anaesthetics Unit include: trauma and intensive care (the Royal London Hospital has the only full helicopter emergency medical service system in London), mode of action of antidepressants and neuromuscular blocking drugs, assessment of open heart surgical pumps and intravascular oxygenators, assessment of anaesthetic monitoring equipment and quality assurance.

For further information contact:

Professor Leo Strunin,
BOC Professor of Anaesthesia,
Anaesthetics Unit,
The London Hospital Medical College,
Whitechapel,
London E1 1BB.
Tel. 071-377 7119.

LONDON: ROYAL POSTGRADUATE MEDICAL SCHOOL AND HAMMERSMITH HOSPITAL

The Department of Anaesthetics at Hammersmith Hospital is unique in the United Kingdom in that the majority of the consultant staff are employed by a university. In 1987, Hammersmith Hospital and Queen Charlotte's Hospital amalgamated to form a Special Health Authority (SHA), and its organization in the United Kingdom is exceptional in that the Professor of Anaesthetics is also the Clinical Director of Services within the SHA. In this sense the organization of anaesthetic services has features in common with academic institutions in other countries, for example, in the U.S.A. The major objective of the RPMS, the Medical Research Council units on the site, the Institute of Obstetrics and Gynaecology and the SHA is the pursuit of teaching and research.

The Department organizes short courses each year. The two courses at Hammersmith are aimed at candidates preparing for the Part 2 and Part 3 of the F.R.C.Anaes. examination. Of the two courses organized at Queen Charlotte's Hospital, one is suitable for candidates preparing for higher diplomas, for example, the F.R.C.Anaes., and the other, while it is of interest to all anaesthetists in obstetric anaesthesia, is aimed at consultants and others with a specialist interest in this field.

In addition, there is an active academic programme at both Hammersmith and Queen Charlotte's Hospitals involving guest lectures, morbidity conferences, presentation of case reports and research in progress by members of the Department, with an ongoing audit programme of anaesthesia, intensive care, resuscitation and critical incidents on a monthly basis.

The Department at Hammersmith Hospital also has a teaching programme for its own junior staff who are preparing for the F.R.C.Anaes. examination. This is ongoing throughout the year. Both the academic lectures and teaching programme are open to the junior staff of the rotational hospitals and to visitors by arrangement.

Each year several undergraduate medical and science students are accepted for elective periods in the Department. Students from both the United Kingdom and European medical schools are welcome.

RESEARCH

There is a wide variety of both clinical and laboratory-based research within the Department. The principal lines of research are:

(1) Studies on the effect of drugs on nociceptive reflexes under the direction of Professor J. G. Whitwam.
(2) Studies on new aspects of ventilation under the direction of Professor J. G. Whitwam and Mr M. K. Chakrabarti.
(3) Studies on the use of spectroscopy in monitoring in anaesthesia and in intensive care, which is a joint project between the Department of Nuclear Magnetic Resonance, under the direction of Professor G. Bydder and Dr D. N. F. Harris.
(4) Studies on closed circuit anaesthesia, fluorine clearance from human brain and the clinical application of anaesthetic injection systems being conducted by Dr G. Lockwood.
(5) Initial clinical trials of new anaesthetic agents and analgesic drugs, under the direction of Dr M. Morgan.
(6) Studies on obstetric anaesthesia and analgesia under the direction of Dr Anita Holdcroft and Dr Barbara Morgan at Queen Charlotte's Hospital.

CLINICAL ACTIVITIES

In addition to routine surgical work, Hammersmith Hospital contains a supraregional centre for hepatobiliary surgery and regional centres for cardiothoracic and renal surgery including renal transplantation. Specialist clinical services on the site include immunology, rheumatology, oncology, haematology, endocrinology, and renal and respiratory medicine. Activity in the Intensive Care Unit, under the direction of Dr Jean Lumley reflects the wide variety of patients treated at Hammersmith Hospital.

For further information contact:

Professor J. G. Whitwam,
Department of Anaesthetics,
Royal Postgraduate Medical School,
Hammersmith Hospital, Du Cane Road,
London W12 0NN.
Tel. 081-740 3289.
Fax 081-749 9974.

LONDON: ST BARTHOLOMEW'S HOSPITAL

There is an active academic unit within the Anaesthetics Department at St Bartholomew's Hospital. It is staffed by three senior lecturers, one lecturer, two research registrars, five technicians and a secretary. The unit is based in the well equipped Anaesthetics Laboratory with adequate office accommodation. There is a seminar room, library and computer room attached to the Department of Anaesthetics. Weekly academic departmental meetings, twice-weekly seminars for junior staff and regular morbidity and mortality meetings are held.

RESEARCH

Both clinical and non-clinical research is carried out by the Anaesthetics Laboratory, often involving junior clinical staff but *only* those with F.R.C.Anaes.. Current projects include:

(1) Studies related to the effects of haemodynamic support on oxygen transport/utilization and outcome in intensive care patients, under the direction of Dr C. J. Hinds and Dr J. D. Watson.
(2) Toxicological and epidemiological studies of smoke inhalation injury, under the direction of Dr R. M. Langford.
(3) Studies of the hormone, insulin-like growth factor, its binding proteins and proteases in relation to changes in response to cardiac and major abdominal surgery and changes in response to critical illness, under the direction of Dr C. J. Hinds and Dr R. M. Langford and in collaboration with Professor J. A. H. Wass, Department of Endocrinology, St Bartholomew's Hospital.
(4) Studies of the abnormalities of neuromuscular function in intensive care patients under the direction of Dr C. J. Hinds.
(5) Studies of the abnormalities of bone marrow morphology and function in critical illness, under the direction of Dr C. J. Hinds.

TEACHING

There is a full programme of undergraduate and postgraduate teaching, undertaken jointly by the Academic and Clinical Units.

The Academic Unit is also active in the organization of the North London Parts 1 and 3 F.R.C.Anaes. courses, and in the St Bartholomew's/Whittington Hospitals Crammer for the F.C.Anaes. Part 3 examination.

For further information contact:

Dr Richard Langford,
Director, Anaesthetics Laboratory,
St Bartholomew's Hospital,
London EC1A 7BE.
Tel. 071-601 7524/7526.
Fax 071-601 7528.

LONDON: ST GEORGE'S HOSPITAL MEDICAL SCHOOL

Professor G. M. Hall was appointed to the Foundation Chair of Anaesthesia in July 1992.

For further information contact:
Professor G. M. Hall,
Department of Anaesthesia,
St George's Hospital,
Blackshaw Road,
London SW17.

LONDON: ST MARY'S HOSPITAL MEDICAL SCHOOL AND IMPERIAL COLLEGE OF MEDICINE

The Department of Anaesthetics of Imperial College of Medicine has laboratory and office accommodation at St Mary's Hospital, Paddington, West London and in Northwick Park Hospital, Harrow, Middlesex. At both sites basic science as well as clinical research is undertaken and medical students are given an introductory course in anaesthetics. Associated teaching hospitals include the Central Middlesex and Ealing Hospitals.

RESEARCH

There are close links with the Anaesthetic Research Unit of the Department of Biophysics in Imperial College in South Kensington; this augments the basic science research of the Department. The recruitment, from a senior post in the pharmaceutical industry, of Dr George Lees to a lectureship in the molecular mechanisms of drug action on the St Mary's site has also strengthened the Department's research potential in basic science. George Lees, an experienced molecular biologist, is developing a Departmental Unit of Molecular Pharmacology. Cell culture techniques and patch clamp studies are currently used to determine the influence of anaesthetics on cell signalling pathways.

All clinical members of the Department are involved in a variety of phase 1–4 clinical trials. Recent work has included trials with a non-depolarizing relaxant with an onset time equal to or less than that of suxamethonium, an opioid with a very short elimination half-life and a long-acting opioid antagonist.

The Academic Department of Surgery at St Mary's has the greatest experience of major laparoscopic surgical procedures of any unit in the country and the anaesthetic issues associated with minimally invasive surgery are being studied by a team under Dr Michael Platt, Senior Lecturer at St Mary's.

The expanding Unit headed by Drs D. E. F. Newton and Christine Thornton in Northwick Park continues to develop and refine the technique of monitoring auditory evoked potentials in order to determine depth of anaesthesia and elucidate aspects of the neurophysiology of analgesia and hypnosis.

TEACHING AND SERVICE ACTIVITIES

There is integration of the Academic and Clinical Departments in teaching, both undergraduate and postgraduate, and in supporting a varied service commitment which incorporates all major surgical specialties. Day release courses are organized on both sites in order to help trainees prepare for Parts 2 and 3 of the F.R.C.Anaes.

For further information contact:
Professor R. M. Jones,
Department of Anaesthetics,
St Mary's Hospital,
London W2 1NY.
Tel. 071-725 1681.
Fax 071-725 6425.

LONDON: UNITED MEDICAL AND DENTAL SCHOOL OF GUY'S AND ST THOMAS'S HOSPITALS

The United Medical and Dental School of Guy's and St Thomas's Hospitals is the largest institution in London University after Imperial College and University College. The Medical School encompasses two campuses, one at Guy's and the other at St Thomas's Hospital, about two miles apart. The Division of Anaesthetics comprises Departments of Anaesthetics on each campus. A course of lectures on basic principles, applied pharmacology and pharmacology of anaesthesia, sedation, resuscitation, and pain relief is given to medical students in their second clinical year. A course on resuscitation is also provided. About two weeks are spent by each student learning techniques in anaesthesia and resuscitation.

GUY'S HOSPITAL

The Department of Anaesthetics at Guy's Hospital is situated on the second floor of New Guy's House where there are offices and laboratories. Staff consist of a professor, three senior lecturers, a lecturer, research staff and a technician. Guy's provides anaesthetic services to the Guy's–King's–Maudsley Neurosurgical Unit at De Crespigny Park, Denmark Hill, London SE5 8AZ.

RESEARCH

The research activities of the department are directed towards a broad range of subjects. Of special interest is research into the safety of anaesthesia, recovery from anaesthesia, and the treatment of acute and chronic pain. Of present special interest is research into new volatile anaesthetic agents, muscle relaxants and sedative drugs.

For further information contact:
Professor A. P. Adams,
Department of Anaesthetics,
Guy's Hospital,
London Bridge,
London SE1 9RT.
Tel. 071-955 4047.

ST THOMAS'S HOSPITAL

Academic staff in this hospital comprise a Professor of Obstetric Anaesthesia and a lecturer who is a senior registrar on rotation, together with other soft-funded posts. Day-release courses for all three parts of the F.R.C.Anaes. are run by the Department. There is one laboratory within this Department and another within the operating theatre complex.

RESEARCH

Both laboratory and clinical research are carried out. Laboratory research involves pharmacokinetics and placental drug transfer and, in collaboration with the UMDS Department of Physiology, research in the fields of selective ion monitoring and neurophysiology. Clinical research is carried out in obstetric anaesthesia and analgesia, postoperative and chronic pain.

For further information contact:
Professor Felicity Reynolds,
Anaesthetic Department,
St Thomas' Hospital,
Lambeth Palace Road,
London SE1 7EH.
Tel. 071-928 9292 (ext. 3215).
Fax 071-633 9910.

LONDON: UNIVERSITY COLLEGE AND MIDDLESEX SCHOOL OF MEDICINE

The Academic Sub-Department of Anaesthetics wa founded in 1989 with the appointment of a Clinical Senior Lecturer, as a part of Department of Surgery. The Academic Sub-Department is sited in the Middlesex Hospital and is closely integrated with the Bloomsbury Anaesthetic Department, an amalgamation of the Middlesex Hospital and University College Hospital Anaesthetic Departments. The Clinical Senior Lecturer has clinical duties in the St Peter's Group of Hospitals, now resited in the Middlesex Hospital. The NHS Consultant and junior staff have free access to the research facilities provided by the Anaesthetic Sub-Unit. Postgraduate teaching in Bloomsbury is a joint responsibility of the Academic Sub-Unit and the NHS Department. Teaching of undergraduates is also organized by the Academic Sub-Unit and undertaken by all members of the joint department.

The Senior Registrars in Bloomsbury rotate through the Academic Sub-Unit on a three-month basis. There are two Post-Fellowship Registrar Posts of one year each with a 50% clinical commitment to the NHS and 50% research time.

RESEARCH

In its two-year history, the Sub-Department has established links with the basic science Departments of University College London. Research projects are underway involving a combined approach to understanding and improving the management of postoperative pain and an insight into the mechanisms of high frequency jet ventilation.

The Association with the St Peter's Group of Hospitals and the Institute of Urology have led to a number of projects investigating the physiological changes occurring during TURP.

For further information contact:

Dr L. M. Bromley,
Senior Clinical Lecturer in Anaesthetics,
Academic Sub-Department of Anaesthesia,
Room 103,
The Middlesex Hospital,
Mortimer Street,
London W1N 8AA.
Tel. 071-636 8333 (ext. 4017).

MANCHESTER

The Medical School of the University of Manchester admits 200 preclinical students per year, with an additional intake of 75 clinical students each year from the University of St Andrews. There is a large central Medical School building (the Stopford Building) and three University Teaching Hospitals attached to the Medical School—the Manchester Royal Infirmary, the University Hospital of South Manchester (Withington Hospital and the Christie Hospital) and Hope Hospital, Salford. Four members of the medical staff hold honorary consultant appointments with the National Health Service. These are the professor, two senior lecturers, and the lecturer in paediatric anaesthesia. Two lecturers in anaesthesia are granted honorary senior registrar status. A non-clinical senior lecturer holds a joint appointment with the Department of Anaesthesia and the Department of Physiological Sciences.

Departmental infrastructure consists of one research associate, one-and-a-half technicians, two full-time secretaries and three part-time secretaries. In addition, a principal grade physicist, a physicist and two physics technicians are seconded to the Department from the North Western Regional Health Authority Regional Physics Department. The physics staff are funded using North Western Regional research infrastructure funds. The bulk of the office and laboratory accommodation used by the Department is located at Withington Hospital but, in addition to some space at the other two teaching hospitals, there is laboratory space in the School of Biological Sciences at the Stopford Building.

A contribution is made by members of the Department to undergraduate teaching at the start of the first preclinical year, with instruction in resuscitation and first-aid. A general introduction to anaesthesia in relation to the basic sciences is given during the first clinical year. During this time the students are attached to anaesthetists in the operating theatre for one week. During the second clinical year, students work mainly in peripheral hospitals within and beyond the boundaries of the North Western Regional Health Authority. Students are attached for one week to anaesthetists during this time for practical instruction in anaesthesia. Revision is provided in the final year with additional allocation on an optional basis. Elective periods may be taken in anaesthesia, both in Manchester and elsewhere. During their first clinical year, students also receive five formal lectures. These include topics such as Care of the Unconscious Patient; Postoperative Analgesia, Preoperative Assessment, Acid Base Balance, and Respiratory Failure.

Postgraduate courses are arranged for the Part 2 and the Part 3 F.R.C.Anaes. examination on both a day-release basis and weekly intensive revision courses. Part 1 F.R.C.Anaes. courses are organized by the members of the National Health Service staff in regional and teaching centres. The University staff contribute to these courses. The University Department is represented by members of its staff on the regional anaesthesia training committees and the Regional Sub-Committee in Anaesthesia.

The importance of training in the experimental method as an essential component of the clinical training of every senior registrar is stressed. Senior registrars are offered the opportunity to obtain research experience under supervision, either in a clinical or laboratory setting. Laboratory studies are usually carried out in pharmacology and in association with physicists working in the University Department. Opportunities for research are arranged on a day-release basis or by temporary attachments to the University Department during the higher professional training programme. Emphasis is placed on continuing education and Departmental meetings are therefore arranged to which senior registrars and consultants are invited. The University Department maintains a regular communication with consultants in charge of training throughout the region (college tutors), and these consultants also assume responsibility for the administration of undergraduate training in their hospitals.

RESEARCH

The research interests of the Department include clinical and laboratory studies of analgesic and relaxant drugs, the performance of anaesthetic breathing systems and the measurement of the depth of anaesthesia.

For further information contact:

Professor T. E. J. Healy,
Department of Anaesthesia,
Withington Hospital,
Manchester M20 8LR.
Tel. 061-447 3863.
Fax 061-447 3865.

NEWCASTLE-UPON-TYNE

The University Department of Anaesthesia was founded in 1948 and is now co-sited with the Department of

Anaesthesia within the new ward block of the Royal Victoria Infirmary, Queen Victoria Road, Newcastle. The members of the Department comprise the professor, a senior lecturer, a first assistant, a non-clinical lecturer and a secretary. A senior technician heads a team of three other technicians.

Undergraduates receive a lecture course in anaesthesia during their fourth year and are attached to the department for two weeks in their final year. During this attachment they spend most of their time in theatre learning practical skills. In addition there are seminars which cover the areas of preoperative assessment, general anaesthesia, anaesthetic pharmacology and physiology. They also receive formal training in cardiopulmonary resuscitation and intubation.

Anaesthetists also contribute regularly to formal lecture courses for undergraduates in pharmacology, respiratory and circulatory diseases, anaesthesia, and dental pharmacology. The department is regularly host to undergraduates on elective attachment from other universities, often from abroad, and to students undertaking the intercalated B.Med.Sci. degree.

The department organizes the Postgraduate Institute for Medicine and Dentistry day-release course intended for trainee anaesthetists preparing for the Part 2 F.R.C.Anaes. examination which extends over three months in the academic year and contributes to the Part 3 F.R.C.Anaes. course run by the Postgraduate Institute. There is also a more informal monthly academic meeting intended for discussion of research for post-fellowship trainees.

RESEARCH

The current Departmental research interests encompass the areas of pharmacokinetics of opioids, muscle relaxants and induction agents.The Department has good laboratory facilities including chromatography, radioimmunoassay, bioassay and computing facilities. There are facilities for a full range of physiological measurements. All these are available to other researchers in the area, and assistance and supervision are afforded to trainees undertaking research projects. Further mainframe computing facilities are provided by the University.

For further information contact:

Professor C. J. Hull,
Department of Anaesthesia,
Royal Victoria Infirmary,
Newcastle-upon-Tyne NE1 4LP.
Tel. 091-222 6980 or 091-232 5131 (ext. 24910).
Fax 091-261 1182.

NOTTINGHAM

The University Department of Anaesthesia in Nottingham occupies offices and laboratories adjacent to the NHS Department, operating theatres and Intensive Therapy Unit in University Hospital. This hospital forms part of the Queen's Medical Centre complex, which incorporates both the preclinical and clinical parts of the Medical School, and there is easy access to all other departments and also to the excellent Medical Library. The medical staff includes a professor, two senior lecturers, two lecturers at senior registrar grade and one lecturer at registrar grade. In addition, there are three research fellows. The academic staff are supported by two technicians and a secretary.

Postgraduate trainees are introduced to anaesthesia through a special trainee programme. Anaesthetic practice is fully supervised for this supernumerary six-month senior house officer appointment. Time is allocated for library preparation for twice-weekly tutorial sessions. Senior house officers then join a rotational scheme which includes experience in District General Hospitals at Derby and Mansfield. Registrars are appointed to three-year rotational posts; one year is spent in a District General Hospital (Derby, Mansfield or Lincoln) and the remaining two years in Nottingham, where the training programme includes expérience in anaesthesia for all the surgical specialties, and in intensive care at University Hospital and City Hospital.

There is close co-operation with the Directorates of Anaesthesia in the organization of the block (one-week) courses for all parts of the F.R.C.Anaes. examination; these courses are co-ordinated with those in Leicester and Sheffield so that a block course is held at one of the teaching centres in the Trent Region before each examination. The expertise of staff in other departments of the Medical School is used extensively, particularly in the Part 2 course.

Higher professional training is arranged by a Steering Committee, and includes rotations to Derby, Mansfield, Lincoln and the Cardiothoracic Unit in Leicester as well as rotations through all the major specialties within Nottingham. Overseas secondments are available for some senior registrars.

There are weekly tutorial/journal club meetings for all junior anaesthetic staff and a weekly departmental meeting for all anaesthetists.

Undergraduates spend one week in full-time attachment to the clinical teachers in the operating theatres and intensive care unit and receive a series of lectures on anaesthesia, perioperative care and intensive therapy. Students may also undertake an elective period of training in anaesthesia.

RESEARCH

Research interest is directed mainly in four areas:

(1) Studies of awareness during anaesthesia.
(2) Investigations into the effects of anaesthetic and analgesic agents on colonic contractility and blood flow.
(3) Studies of gastrointestinal motility, absorption and blood flow in the critically ill.
(4) *In vitro* investigations of transmitters in the non-cholinergic, non-adrenergic nervous system.

In addition, many clinical investigations instituted or undertaken by consultants or trainees are supported. There is an opportunity for senior registrars to spend six months in the University Department to undertake research, and both formal and informal tuition is given in research methodology.

For further information contact:

Professor A. R. Aitkenhead,
University Department of Anaesthesia,
University Hospital,
Queen's Medical Centre,
Nottingham NG7 2UH.
Tel. 0602-709229 (direct line).
Fax 0602-700739.

OXFORD

The Nuffield Department of Anaesthetics is a joint University/NHS Department which is responsible for the anaesthetic services in the Oxfordshire Health Authority. The academic department is split between the Radcliffe Infirmary, the John Radcliffe and the Churchill Hospital sites, and consists of a professor, three clinical readers, a university lecturer in clinical physics, a clinical lecturer, a research registrar funded by the Wellcome Trust, two electronics engineers, a mathematician, an administrator, two secretaries, a part-time librarian and three technicians. The University also administers the NHS physiological measurement service which is run by a senior physicist and five technicians.

The NHS staff consists of 27 consultants, 10 senior registrars, 16 SHO/registrars, an administrator and two secretaries, whilst the Oxford Regional Pain Relief Unit has its own administrator and one whole-time and one part-time secretary. Most of the junior staff rotate to Regional District General Hospitals. The Department is also responsible for general, paediatric and neurological intensive care units together with the Oxford Regional Pain Relief Unit. The Department runs short courses for Parts 1 and 2 of the F.R.C.Anaes. and tutorials for those taking Part 3. There is a formal academic programme every Friday which includes an ITU ward round, x-ray conference and seminar and there are regular Departmental meetings featuring guest lectures, research presentations and morbidity meetings. There is an active undergraduate teaching programme and a number of undergraduates from other universities spend elective periods in the Department. The Department also runs a number of short residential courses on various aspects of anaesthesia and research.

RESEARCH

There are usually between 15 and 20 graduate scientists, medically qualified research workers and research nurses in the Department at any one time. The main lines of research are:

(1) Respiratory: development of new techniques for measuring ventilation/perfusion inequalities in the lung; effect of new techniques of respiratory support on the development of lung damage; the use of high frequency oscillation to measure lung mechanics; the efficacy of nitric oxide in pulmonary hypertension; long-term monitoring of sleep, respiration and cardiovascular function during the pre- and postoperative periods; role of cytokines in respiratory failure.
(2) Cardiovascular: interactions between anaesthesia, cardiovascular drugs and myocardial ischaemia; magnetic resonance studies of the relationship between mechanical function and high energy phosphates in the ischaemic heart; effects of anaesthetic agents on left ventricular diastolic function; effects of myocardial ischaemia on diastolic function; prevalence of silent ischaemia in surgical patients. Noninvasive methods of assessing cardiovascular function during anaesthesia and intensive care.
(3) Pharmacology: the measurement of the effect and tissue concentrations of both old and novel analgesics; clinical trials of analgesic drugs; the pharmacokinetics of hypnotics and anaesthetic-related drugs; the modification of the stress response by analgesic and other drugs administered by various routes; effects of anaesthetic agents on ion fluxes in myocytes and neuronal preparations.
(4) The treatment of intractable pain.
(5) Molecular sensors: the development of new electrochemical sensors for O_2, CO_2, inhalation anaesthetics; the development of a lactate sensor; the use of electrochemical techniques for measurement of drugs and intermediary metabolites *in-vitro*.
(6) Physics: the development of new anaesthetic apparatus and measuring equipment.
(7) Electronics: the application of microprocessor techniques to clinical measurement and control of anaesthesia.

For further information contact:
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Nuffield Department of Anaesthetics,
Radcliffe Infirmary,
Oxford OX2 6HE.
Tel. 0865-224847/224770 (direct line).
Fax 0865-794191.

SHEFFIELD

The University Department of Anaesthesia in Sheffield is based in the Medical School adjacent to the Royal Hallamshire Hospital. There is a strong working relationship with the Division of Anaesthetics which represents all the hospital departments of anaesthesia within the city including the Royal Hallamshire Hospital, the Northern General Hospital, the Jessop Hospital for Women and the Children's Hospital. All 36 NHS consultants are honorary clinical lecturers and contribute to the undergraduate and postgraduate teaching. The training of the 18 higher and 36 general professional trainees is supervised jointly.

The University Department staff includes the Professor and Senior Lecturer, six lecturers (three honorary senior registrars and three honorary registrars), research nursing sisters, Ph.D. students and full technical and secretarial assistance.

The Department provides comprehensive day-release and intensive courses for all three parts of the F.R.C.Anaes. examination throughout the year. Undergraduate teaching in Sheffield entails a six-week (half-day) attachment, consisting of lectures, tutorials and clinical work for all final year students. Students are also offered an intercalated B.Med.Sci. degree course of one year. Postgraduate courses leading to an M.Med.Sci. degree are available in the scientific basis of anaesthesia in dentistry and surgical sciences (anaesthesia).

RESEARCH

An active research programme is pursued by the department with many projects having an applied pharmacology basis. The main areas of research interest for the department include drug absorption, anaesthesia and drug metabolism, i.v. anaesthesia, methods of providing analgesia and assessment of perioperative risk. Specific projects on transdermal analgesia, the mechanism of onset of i.v. anaesthesia and the use of continuous ambulatory ECG monitoring in the perioperative period are being developed. A joint research programme with the Department of Control Engineering on development of feedback control of infusion anaesthesia has been started.

Recent involvement with the Royal Hallamshire Hospital ITU and the University Medical Physics Department has led to the evaluation of anaesthetic and intensive care equipment. Other collaborative research involves work with the University Departments of Pharmacology and Therapeutics, Obstetrics and Gynaecology, Radiology and Surgery. The Department of Animal and Plant Sciences is currently involved with the Department in work on a new model for measuring anaesthetic potency.

For further information contact:
Professor C. S. Reilly,
University Department of Anaesthesia,
University of Sheffield Medical School,
Beech Hill Road,
Sheffield S10 2RX.
Tel. 0742-700295 (direct).
Fax 0742-728 622.

SOUTHAMPTON

The Shackleton Department consists of both University and NHS staff. Its main site is in the General Hospital but the Department provides clinical services throughout all the hospitals in Southampton. The range of services includes all those found in a District General Hospital together with the regional services for neurosurgery, paediatric, thoracic and cardiac surgery. The Department is recognized under Schedule 1 of the College's hospital recognition procedures.

Day-release and block-release courses of one-week duration are organized for trainees in Wessex for all parts of the F.C.Anaes. examinations. The courses are open to trainees from outside the region.

Undergraduate training covers resuscitation, pre- and postoperative care and pain control, and the elements of anaesthesia. Elective periods in anaesthesia of two or three weeks duration are also used. Up to four students each year spend their fourth year in the department for a study-in-depth.

RESEARCH

The main current interests include aspects of anaesthetic safety, involving the use of neuromuscular blocking drugs, factors affecting cerebral blood flow and the outcome of intensive care.

For further information contact:
Professor J. Norman,
Shackleton Department of Anaesthetics,
Department of Anaesthetics,
University of Southampton,
General Hospital,
Tremona Road,
Southampton SO9 4XY.
Tel. 0703-796137 (direct).
Fax 0703-704062.

NHS Postgraduate Training Areas and Hospital Telephone Numbers

EAST ANGLIAN REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Cambridge Health District			
Addenbrooke's Hospital 0223–245151	18	4 (+1 Lecturer)	5/3
East Suffolk Health District			
Ipswich Hospital 0473–712233	14	1† (+1 P/T SRs)	3*/4
Great Yarmouth and Waveney	9	—	1/4
Huntingdon Health District			
Hinchingbrooke Hospital 0480–456131	6.5	—	1*/2
Specialist Hospital Papworth Hospital 0480–830541 (Cardiothoracic surgery)	4.5	1†	2*/2
Norwich Health District			
Norfolk and Norwich Hospital, Norwich 0603–628377	17.5	2†	4‡/8
Peterborough Health District	14	1†	4§/5
West Norfolk & Wisbech Health District			
Queen Elizabeth Hospital, King's Lynn 0553–766266	7	1†	3*/3
West Suffolk Health District			
West Suffolk Hospital, Bury St. Edmunds, 0284–763131 Newmarket General Hospital 0638–665111	9 (+2 P/T)	1†	–/4

†Rotating with Cambridge. *1 registrar rotates with Cambridge. ‡2 registrars rotate with Cambridge. §1 registrar relates with Leicester, 1 with Cambridge.

Regional Educational Adviser:
Dr C. H. Woollam, Department of Anaesthesia, Norfolk and Norwich Hospital, Brunswick Road, Norwich NR1 3SR. Tel. 0603–628377.

MERSEY REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Liverpool Health District Royal Liverpool Hospital* 051–706 2000 (Fax 051–709 2247) (Maxillo-facial; Head and Neck; Renal Transplant; Renal Dialysis; ITU) Liverpool Dental Hospital* 051–706 2000 St Paul's Eye Hospital* 051–260 8787 Sefton General Hospital 051–733 4020	16 (4 attached to the University Department)	5† (1 attached to the University Department, 1 to ITU)	7†/9
Broadgreen Hospital* 051–228 4878 (Fax 051–254 2070) Cardiothoracic Centre 051–228 1616 (Fax 051–220 8573) Broadgreen (University) Mill Road Maternity Hospital 051–260 8787	14	3† 2 (Hon.)	7†/2
Liverpool Maternity/Women's Hospital*	5	1†	4†
Royal Liverpool Children's Hospital*, Alder Hey 051–228 4811 (Paediatric and Neonatal)	10	3†	3†(4†)

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Southport and Formby			
Southport and Formby District General Hospital 0704–547471 Christiana Hartley Maternity Hospital 0704–547471	6	—	2†/2
South Sefton			
Walton Hospital* 051–525 3611 (Neurosurgical; Pain Relief) Fazakerley Hospital 051–525 5980	17 (6 P/T)	4†	8†/7
Wirral			
Arrowe Park Hospital 051–678 5111 Clatterbridge Hospital 051–334 4000 (Radiotherapy)	11 (3 P/T)	2†	6†/7
Chester			
Royal Infirmary 0224–365000 Countess of Chester Hospital 0244–365000	7 (+2 P/T)	2†	2†/5
Crewe			
Leighton Hospital 0270–255141	7	—	2†/6
Macclesfield Health District			
Macclesfield Hospital 0625–21000 Macclesfield Infirmary 0625–21000 Parkside Hospital 0625–21000	5	—	2†/3
Warrington			
Warrington District General Hospital	9	—	2†/4
St Helen's and Knowsley			
Whiston Hospital 051–426 1600 (Burns and Plastics Unit) St Helen's Hospital 0744–26633	9 (1 P/T)	2†	4†/6

*Associated with a university department. †Rotating. From 1 October 1991 all registrar posts, with the exception of 3 post-fellowship appointments at RLCH, Alder Hey, will be incorporated into a Regional Rotational Training Scheme.

Regional Educational Adviser:
Dr D. A. Nightingale, Alder Hey R.L.C.H., Eaton Road, West Derby, Liverpool L12 2AP. Tel. 051–228 4811; Fax 051–228 0328.

NORTHERN REGION HEALTH AUTHORITY

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Newcastle			
Royal Victoria Infirmary* 091–232 5131	15	7	10
Newcastle General Hospital* 091–273 8811	14	6	10
Freeman Hospital* 091–284 3111 (Fax 091-213 1968)	17	6	9
Hartlepool			
Hartlepool General Hospital 0429–2666 549	5	—	5
North Tees			
North Tees General Hospital, Stockton-on-Tees 0642–672122	7	—	5
South Tees			
Middlesbrough General Hospital 0642–850222	18	4	9
East Cumbria			
Cumberland Infirmary, Carlisle 0228–23444	11	—	4

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
West Cumbria			
Whitehaven Hospital 0946–3181	5	—	3
South Cumbria			
Furness General Hospital, Barrow-in-Furness 0229 870870	6	—	—
Darlington			
Darlington Memorial Hospital 0325–380100	5	1	7
Durham			
Dryburn Hospital, Durham 091–3864911	5	—	4
North West Durham			
Shotley Bridge General Hospital 091–503456	6	—	3
South West Durham			
Bishop Auckland General Hospital 0388–604040	4	—	3
Gateshead			
Queen Elizabeth Hospital 091–487 8989	7	—	6
Northumberland			
Ashington Hospital 0670–812541	6	—	4
Hexham General Hospital 0434–606161	4	—	—
North Tyneside			
Preston Hospital, North Shields 091–259 6660	5	—	3
South Tyneside			
South Shields General Hospital 091–4561161	5	—	5
Sunderland			
Sunderland District General Hospital 091–565 6256 (Fax 091–514 0220)	17	1	10

*Associated with a university department.

Regional Educational Adviser :
Dr J. Baldasera, Department of Anaesthesia, Sunderland District General Hospital, Kayll Road, Sunderland, Tyne-and-Wear SR4 7TP. Tel. 091–565 6256 (ext. 2446/2447).

NORTH WESTERN REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Bolton			
Bolton General Hospital 0204–22444	9	—	7
Bolton Royal Infirmary 0204–22444			
Blackburn			
Blackburn Royal Infirmary 0254–63555	9	—	9
Blackpool			
Victoria Hospital 0253–34111	14	1	10
Burnley			
Burnley General Hospital 0282–25071	7	—	6
Bury			
Bury General Hospital 061–764 6081	6	—	7
Lancaster			
Royal Lancaster Infirmary 0524–65944	10	1	8

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Manchester Central			
Manchester Royal Infirmary* 061–276 1234	22	8	15
Manchester North			
North Manchester General Hospital 061–795 4567	14	4+1‡	8
Manchester South			
University Hospital of South Manchester* 021–275 6666	14	4+1†	12
Wythenshawe Hospital 061–998 7070	12	3	9
Oldham			
Oldham and District General Hospital 061–624 0420	11	—	7
Oldham Royal Infirmary 061–624 0420			
Preston			
Royal Preston Hospital 0772–716565	18	1	13
Chorley Trust Hospital 0257–261222	1	—	—
Rochdale			
Rochdale Infirmary 0706–7777	6	—	5
Salford*			
Hope Hospital 061–789 7373	18	5[x]+1‡	10
Salford Royal Hospital 061–834 8656			
Stockport			
Stepping Hill Hospital 061–483 1010	10	1	9
Stockport Infirmary 061–480 7441			
Tameside			
Tameside General Hospital 061–330 8373	8	—	6
Trafford			
Trafford General Hospital 061–748 4022	6	—	7
Ormskirk			
Ormskirk and District General Hospital 0695–75471	5	—	4
Wrightington Trust Hospital 0695–75471	4	—	—
Wigan			
Royal Albert Edward Infirmary 0942–44000	11	—	15

*Associated with a university department. ‡Permanently on paediatric duty.
†University lecturer with SR standing. [x]Two assigned in rotation to Department of Neurosurgery and Pain Clinic.
Associate specialists are also employed by some Health Authorities in the North West Region.
These figures do not include junior doctors employed under the DHSS arrangements for part-time training.

Regional Educational Adviser:
Dr W. A. Wallbank, Department of Anaesthesia, Withington Hospital, West Didsbury, Nell Lane, Manchester M20 8LE. Tel. 061–445 8111.

OXFORD REGION

Hospital	Consultants	Senior registrars	Registrars/ SHOs
Stoke Mandeville 0296–315000	10	1	2/6
Wycombe General 0494–26161	7	1	3/5
Horton General Hospital, Banbury 0295–275500	6	—	0/4
Kettering and District General Hospital 0536–410666	8	—	3/5
Northampton General Hospital 0604–34700	9	1 (1 P/T)	4/7

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Milton Keynes Hospital 0908–660033	10	1	1/4 (+1 P/T)
East Berkshire			
Wexham Park Hospital, Slough 0753–633000 Heatherwood Hospital, Ascot 0344–23333	11	—	15/5
Oxford			
John Radcliffe Hospital 0865–741166 Radcliffe Infirmary 0865–311188	32	11	10/6
Royal Berkshire Hospital, Reading 0734–875111	13	2	4/8 (+2 P/T)

Regional Educational Adviser:

Dr Colin Blogg, Nuffield Department of Anaesthetics, Radcliffe Infirmary, Oxford OX2 6HE. Tel. 0865–311188.

SOUTH WESTERN REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Bristol and Weston			
Weston-super-Mare General Hospital 0934–636363	5	—	0/5
Bristol Royal Infirmary 0272–230000 Bristol* Weston*	23 (+3)	9 (+1)	11/5
Frenchay*			
Frenchay Hospital, Bristol 0272–701212	13	3	6/2
Southmead*			
Southmead Hospital, Bristol 0272–505050	11 (+1)	2 (+1)	4/4
(Bath)*†			
Royal United Hospital 0225–428331	14	2	3/7
Gloucester and Cheltenham DHAs			
Cheltenham General Hospital 0242–222222 Gloucester Royal Hospital 0452–28555	21	1	6/12
Somerset			
Taunton and Somerset Hospital 0823–333444	10	—	4/4
Yeovil District Hospital 0935–751222	6	—	1/5
Exeter			
Royal Devon and Exeter Hospital 0392–411611	16	2	4/9
N. Devon			
North Devon District Hospital, Barnstaple 0271–22577	7	—	0/4
Plymouth			
Plymouth General Hospital 0752–777111	19	4	7/8
Torbay			
Torbay Hospital, Torquay 0803–614567	11	—	3/5
Cornwall and Isles of Scilly			
Truro Royal Cornwall Hospital 0872–74242 West Cornwall Hospital, Penzance 0872–2382	15	1	3/7

(University staff with comparable status shown in brackets.)

*Associated with a university department. †Bath is officially in Wessex but participates in Avon anaesthetic training programme.

Regional Educational Adviser:

Dr J. W. O'Higgins, Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW. Tel. 0272–282163.

NORTH EAST THAMES REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Barking, Havering and Brentwood			
Harold Wood Hospital 0402–345533	4	—	1/5
Oldchurch Hospital 0708–746090	8	—	3/6
Basildon and Thurrock			
Basildon Hospital (Orsett) 0375–891100 (Basildon) 0268–533911 (St Andrews) 0277–622611	13	2	2/9
Bloomsbury and Islington			
Middlesex Hospital 071–636 8333	12	5	9/4
University College Hospital 071–387 9300	9	5	4/4
Whittington Hospital 081–807 3071	7	1	5/6
Royal National Throat, Nose and Ear Hospital 071–837 8855	6	1	3/—
Royal National Orthopaedic Hospital 081–954 2300	8	1	3/—
City and Hackney			
St Bartholomews 071–601 8888	17	5	13/9
Homerton Hospital 081–985 5555			
St Marks Hospital 071–253 1050			
Enfield			
Enfield District Hospital, Chase Farm 081–366 6600	6	1	3/7
Hampstead			
Royal Free Hospital 071–794 0500	12 (+1)	5	8/3
Haringey			
North Middlesex Hospital 081–807 3071	9	1	4/6
Mid-Essex			
Broomfield Hospital 0245–440761	8	1	3/6
Newham			
Newham General Hospital 071–476 1400	9	3	3/3
North East Essex			
Essex County Hospital, Colchester 0206–853535	8	—	2/8
Redbridge			
King George Hospital 081–554 8911	4	—	4/4
Southend			
Southend Hospital 0702–348911	8	1	5/4
Tower Hamlets			
Royal London Hospital 071–377 7000	11 (+4)	8	8/7
Waltham Forest			
Whipps Cross Hospital 081–539 5522	10	2	6/4
West Essex			
Princess Alexandra Hospitals 0279–444455	8	1	3/8
The Hospital for Sick Children, (GOS) 071–405 9200	11	7	6/—
London Chest Hospital 081–980 4433	4	2	1 (+1)/—
National Hospital for Neurology 071–837 3611	7	5	2 (+1)/—

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Eastman Dental Hospital 071–387 0351	4	1	1/—
Moorfields Eye Hospital 071–253 3411	12	—	3/—

( ) Associated with a university department.

Regional Educational Adviser:
Dr S. Ingram, Department of Anaesthesia, University College Hospital, Gower Street, London WC1E 6AU. Tel. 071–380 9811.

NORTH WEST THAMES REGION

Health Authority and Hospital	Consultants	Senior registrars	Registrars/ SHOs
North Bedfordshire			
Bedford General Hospital 0234–355122 (Fax 0234–218106)	7	—	4/3
South Bedfordshire			
Luton and Dunstable Hospital 0582–491122	9	—	4/4
East Hertfordshire			
Queen Elizabeth II Hospital, Welwyn 0707–328111	5	—	3/3
North Hertfordshire			
Lister Hospital 0438–314333	8	1	3/3
North West Hertfordshire			
St Alban's City Hospital 0727–866122	5	—	3/3
Hemel Hempstead General Hospital 0442–213141		1	3/3
South West Hertfordshire			
Watford General Hospital 0923–244366 (Fax 0923–217440)	5	1	3/3
Barnet			
Barnet General Hospital 081–440 5111	5	1	3/3
Edgware General Hospital 081–952 2381 (Fax 081–732 6807)	7	2	3/4
Harrow			
Northwick Park Hospital 081–864 3232 (Fax 081–423 0046)	10	3	5/5
Hounslow & Spelthorne			
West Middlesex Hospital 081–560 2121 (Fax 081–560 2395)	6	—	4/3
Ashford Hospital 0784–251188 (Fax 0784–264017)	5	—	3/3
Hillingdon			
Hillingdon Hospital 0895–238282	6	1	3/4
Harefield Hospital 089–582 3737	9	2	2/2
Mount Vernon Hospital 0923–826111 (Fax 0923-835803)	5	1	2/2
Ealing			
Ealing Hospital 081–574 2444 (Fax 081–967 5630)	5	1	2/7
Parkside			
St Mary's* 071–725 1556 (Fax 071-725 6425)	13	4	11/8
Central Middlesex Hospital 081–965 5733	7	1	4/3
Riverside			
Charing Cross Hospital 081–846 1234 (Fax 081–846 1111)	12	6	10/6
Westminster Hospital* 081–746 8025 (Fax 081–746 8801)	9	4	6/6

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Special Health Authority			
Hammersmith Hospital* 081–743 2030 (Fax 081-740 3169)	7	9	4/4
Queen Charlotte's Hospital 081–748 4666 (Fax 081–741 1838)	4	1	3/—
Royal Brompton National Heart and Lung Hospitals 071–352 8121 (Fax 071-351 8473)	7	5	4/—
Royal Marsden 071–352 8171	6	3	4/—

*Associated with a university department.

Regional Educational Adviser:
Dr Margaret Clark, Department of Anaesthetics, Edgware General Hospital, Edgware, Middlesex HA8 0AD. Tel. 081–732 6288 (Fax 081–732 6807).

SOUTH EAST THAMES REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Bexley			
Queen Mary's Hospital 081–302 2678	4	—	3/3
Brighton			
Royal Sussex County Hospital 0273–609060	14	3	2/6
Bromley			
Bromley Hospital 081–460 9933	8	1	4/6
Camberwell*			
King's College Hospital 071–326 3154	13 (+2 Hon)	5 (+1 Hon)	9/6
Canterbury and Thanet			
Kent and Canterbury Hospital 0227–766877	15	1	2/10
Thanet District Hospital 0843–225544			
Dartford and Gravesham			
Joyce Green Hospital 0322–227242	8	—	3/6
Eastbourne			
Eastbourne District General 0323–417400	9	1	1/5
Greenwich*			
Greenwich District Hospital 081–858 8141	14	3	6/9
Brook General Hospital 081–856 5555			
Hastings			
Conquest Hospital 0424–755255	7	—	2/3
Lewisham and North Southwark*			
Guy's Hospital 071–955 5000	22 (+2 Hon)	7 (+1 Hon)	8/8
Lewisham Hospital* 081–690 4311			
Maidstone			
Maidstone Hospital 0622–729000	7	—	2/6
Medway			
Medway Hospital* 0634–830000	10	1	2/6
South East Kent			
William Harvey Hospital 0233–633331	9	—	3/6
Tunbridge Wells			
Pembury Hospital 0892–528261	11	1	5/5
Kent and Sussex Hospital 0892–526111			
Queen Victoria Hospital, East Grinstead 0342–410210			

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
West Lambeth*			
St Thomas' Hospital 071–928 9292	13 (+1 Hon)	7	7/6

*Associated with a university department.

Regional Educational Adviser:
Dr P. A. D. Williams, Royal Alexandra Hospital for Sick Children, Dyke Road, Brighton, East Sussex BN1 3JN. Tel. 0273–328145; Fax 0273–736685.

SOUTH WEST THAMES REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Chichester			
St Richard's Hospital, Chichester 0243–788122	7	—	3/5
King Edward VII Hospital, Midhurst			
Croydon			
Mayday Hospital 081–684 6999	11	—	4/8
East Surrey			
East Surrey Hospital 0737–768511	6.7	—	2/4
Kingston & Esher			
Kingston Hospital 081–546 7711	7	1	3/4
Merton and Sutton			
St Helier Hospital 081–644 4343	10 (+0.5 x 1)	2	6/5
Sutton Hospital			
Nelson Hospital			
Queen Mary's Hospital for Children, Carshalton 081–643 3300			
Mid Surrey			
Epsom General Hospital 0372–726100	6	—	2/3
Mid Downs			
Princess Royal Hospital 0444–441881	6	—	2/3
Crawley Hospital 0293–527866	4	—	2/3
North West Surrey			
St Peter's Hospital, Chertsey 0932–872000	7	1	3/4
Richmond, Twickenham and Roehampton			
Queen Mary's Hospital, Roehampton 081–789 6611	6.5	2	3/3
South West Surrey			
Royal Surrey County Hospital 0483–571122	10	1	4/4
St Luke's Hospital, Guildford			
Wandsworth			
St George's Hospital* 081–672 1255	24	9	16/6
Atkinson Morley's Hospital			
West Surrey and North East Hampshire			
Frimley Park Hospital 0276–692777	11	1	3/6
Farnham Hospital			
Worthing			
Worthing Hospital 0903–205111	7	—	3/4
Southlands Hospital 0273–455622			

By October 1992, 44 of the region's registrars will be on rotation from St George's Hospital. The senior registrars based at Queen Mary's Hospital for Children, Carshalton, and Royal Surrey County Hospital, Guildford are on rotation from the Middlesex Hospital and Charing Cross Hospital respectively: all other senior registrars in the region are on rotation from St George's Hospital.
*Associated with a university department.

Regional Educational Adviser:
Dr P. Radford, Queen Mary's Hospital for Children, Carshalton, Surrey SM5 4NR. Tel. 081–643 3300.

TRENT REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Sheffield			
Royal Hallamshire 0742–766222	40 (+1 P/T) (1 Professor, 2 Hon, 1 Senior Lecturer)	12 (+3 Lecturers)	18/18
Northern General 0742–434343			
Children's Hospital 0742–761111			
Jessop Hospital for Women 0742–766333			
Nether Edge Hospital 0742–500222			
Lodge Moore Hospital 0742–630222			
Nottingham			
Eye Hospital	31 (+1 P/T) (+2 Hon, 1 Professor, 2 Senior Lecturers)	9 (+1 Hon)	14/19
General Hospital 0602–481100			
Nottingham City Hospital 0602–691169			
University Hospital 0602–421421			
Leicestershire			
Leicester General 0533–490490	40 (1 Professor +3 Senior Lecturers)	9 (+3 Hon)	14/19 (+4 Hon)
Leicester Royal Infirmary 0533–541414			
Groby Road (Cardiothoracic) 0533–874141			
Glenfield Hospital 0533–871471			
Central Nottinghamshire			
Mansfield District General Hospital 0602–22515	12	1	4/4
King's Mill Hospital 0602–22515			
Harlow Wood (Sub Regional) Orthopaedic Hospital 0623–35431			
Bassetlaw			
Victoria Hospital 0909–472831	4	—	3 (Hon)
Kilton Hospital			
Southern Derbyshire			
Derbyshire Royal Infirmary 0332–47141	17 (1 Senior Lecturer)	2	6/8
Derby City Hospital 0332–40131			
Hospital for Sick Children 0332–47141			
North Derbyshire			
Chesterfield Royal Hospital 0246–277271	13	1	3/4
South Lincolnshire			
Grantham & Kesteven General Hospital 0476–65232	5	—	0/4
Boston Pilgrim Hospital 0205–64801	7	—	1/4
North Lincolnshire			
Lincoln County 0522–512512	13	1	3/4
St George's Hospital Lincoln 0522–512512			
Louth County Hospital 0507–600100			
Rotherham			
Rotherham District General Hospital 0709–820000	9 (+1 P/T)	1	2/5
Barnsley			
Barnsley District General Hospital 0226–730000	8	—	2/4

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Doncaster Doncaster Royal Infirmary 0302–66666	14 (+1 P/T)	1	3/4

Regional Educational Adviser:

Dr J. Cole, Department of Anaesthesia, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2RX. Tel. 0742–766222.

WESSEX REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Southampton Southampton General Hospital* 0703–777222 (including Regional Neurosurgical, Cardiothoracic and Paediatric Units) Royal South Hants Hospital* 0703–634288 Southampton Eye Hospital 0703–638883	23 (+2 Hon)	11 (+1 Hon) (+4 P/T)	10/12
Portsmouth Queen Alexandra Hospital, Cosham 0705–379451 St Mary's Hospital, including Regional Renal Unit, Portsmouth 0705–822331	18	3	7/6
Bournemouth/Poole Bournemouth General Hospital 0202–303626 Royal Victoria Hospital, Boscombe 0202–395201 Poole General Hospital 0202–675100 Royal Victoria Hospital,* Westbourne 0202–761332 Christchurch Hospital 0202–486361	17	2	6/6
Bath Royal United Hospital 0225–428331 St Martin's Hospital 0225 832383	14 (+1 P/T)	2	3/9
Swindon Princess Margaret Hospital 0793–536231	9	1	3/6
Basingstoke and North Hampshire Basingstoke District General 0256–473202 Lord Mayor Treloar Hospital, Alton 0420–82811	9	1	3/5
Winchester Royal Hampshire County Hospital 0962–63535	9	1 (+1 P/T)	1/7
Salisbury Odstock Hospital, including Regional Plastic Unit, 0722–336262 Salisbury General Infirmary 0722–336212	7	1	2/4 (+1 P/T)
Isle of Wight Royal Isle of Wight Hospital, Ryde 0983–524081 St Mary's Hospital, Newport 0983–524081	5	—	—

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Dorchester/Weymouth			
Weymouth & District Hospital 0305–772211 West Dorset Hospital, Dorchester 0305–251150 Dorset County Hospital, Dorchester 0305–263123	5	—	2/2
Jersey			
Jersey General Hospital 0534–59000	4	—	6/0

*Associated with a university department.

Regional Educational Adviser:
Dr A. Dewar, Department of Anaesthesia, Southampton General Hospital, Tremona Road, Southampton SO9 4XY. Tel. 0703–777222.

WEST MIDLANDS

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Hereford			
County Hospital 0432–355444 Hereford General Hospital 0432–355444 Victoria Eye Hospital 0432–355444	6	—	2/3
Worcester			
Worcester Royal Infirmary 0905–353507 (Castle Street and Ronkswood Branches and Worcester Eye Hospital)	9	—	2/4
Kidderminster			
Kidderminster General Hospital 0562–823424	5	—	1/2
Bromsgrove and Redditch			
Alexandra Hospital, Redditch 0577–503030	8	—	2/3
Shropshire			
Royal Shrewsbury Hospital 0743–231122 (inc. Eye, Ear & Throat Hospital) Robert Jones & Agnes Hunt Orthopaedic Hospital, Oswestry 0691–655311	12	1	3/7
Telford District General Hospital 0952–641222	8	—	2/4
Mid-Staffordshire			
Staffordshire District General Infirmary 0785–57731	7	—	2/5
North Staffordshire			
City General Hospital, Stoke North Staffordshire Royal Infirmary, Stoke 0782–715444	22	4.5	7/7
South East Staffordshire			
Burton District Hospital Centre 0283–511511	7	—	2/3
North East Warwickshire			
George Eliot Hospital, Nuneaton 0203–384201 Manor Hospital, Nuneaton 0203–384201	9	—	2/4
Hospital of St Cross, Rugby (NHS Trust) 0788–572831	4	—	1/2

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
South Warwickshire			
Stratford-upon-Avon Hospital 0789–205831 Warneford General Hospital, Leamington 0926–427121 South Warwick Hospital, Warwick 0926–495321	8	—	3/3
Birmingham East			
East Birmingham Hospital (NHS Trust) 021–766 6611	11	3	5/8
Birmingham North			
Good Hope District General Hospital 021–378 2211	5	—	3/4
Birmingham South			
Birmingham Children's Hospital 021–454 4851 Birmingham Dental Hospital* 021–236 8611 Birmingham & Midland Hospital for Women 021–772 1101 General Hospital, Birmingham 021–236 8611 Queen Elizabeth Medical Centre* 021–472 1311 (inc. Queen Elizabeth Hospital and Birmingham Maternity Hospital)	27 (inc. 2 Hon)	14 (inc. 5 Hon)	13/5
Birmingham Accident Hospital 021–643 7041	3	2	2/1
Royal Orthopaedic Hospital 021–476 3111 Selly Oak Hospital 021–472 5313 Sorrento Maternity Hospital 021–449 4242	11	1	5/4
Birmingham West			
Birmingham & Midland Eye Hospital 021–236 4911 Dudley Road Hospital 021–554 3801	13	3.5	6/5
Coventry			
Coventry & Warwickshire Hospital 0203–224055 Walsgrave Hospital (NHS Trust) 0203–602020	21	4	7/7
Dudley			
Russells Hall Hospital 0384–52243 Corbett Hospital, Stourbridge 0384–390390 Guest Hospital, Dudley 0384–56966 Wordsley Hospital, Stourbridge 0384–288778	12	—	4/8
Sandwell			
Sandwell District General Hospital 021–553 1831 Midland Centre for Neurology & Neurosurgery, Smethwick 021–558 3232	10	2	1/4
Solihull			
Solihull Hospital 021–711 4455	6	—	0/4
Walsall			
Walsall District General Hospital (NHS Trust) 0922–721172	7	—	3/3
Wolverhampton			
New Cross Hospital 0902–307999 Royal Hospital 0902–351532 Wolverhampton & Midland Counties Eye Infirmary 0902–326731	11	2	4/7

*Associated with a university department.

Regional Educational Adviser:
Dr R. S. C. Howell, Department of Anaesthesia, Walsgrave Hospital, Coventry CV2 2DX. Tel. 0203–602020.

YORKSHIRE REGION

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Leeds Western District			
Leeds General Infirmary 0532–432799	17	7	8/7
Wharfedale Hospital 0943–465522	3		—/1
Leeds Eastern District			
St James's University Hospital 0532–433144	17	7	6/7
Killingbeck Hospital 0532–648164	6	1	—/3
Airedale District			
Airedale General Hospital 0535–652511	5	—	1/2
Bradford District			
Bradford Royal Infirmary 0274–42200	16	3	6/9
Calderdale District			
Halifax General Hospital 0422–57171	6	—	2/4
Dewsbury District			
Dewsbury District Hospital 0924–465111	7	—	1/3
Grimsby District			
Grimsby District General Hospital 0472–74111	7	—	2/3
Harrogate District			
Harrogate District General Hospital 0423–885959	5	—	1/4
Huddersfield District			
Huddersfield Royal Infirmary 0484–22191	7	—	2/2
Hull and East Yorkshire			
Hull Royal Infirmary 0482–28541	20	2	8/10
Northallerton District			
Friarage Hospital 0609–779411	3	—	—/2
Pontefract District			
Pontefract General Infirmary 0977–792361	7	—	2/5
Scarborough District			
Scarborough Hospital 0723–368111	6	—	1/5
Scunthorpe District			
Scunthorpe General Infirmary 0724–843481	6	—	—/3
Wakefield District			
Pinderfields General Infirmary 0977-375217	9	1	2/5
York District			
York District Hospital 0904–31313	10	2	3/6

Regional Educational Adviser:
Dr J. B. Dyson, St James's University Hospital, Beckett Street, Leeds LS9 7TF. Tel. 0532–433144.

WALES

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Gwynedd			
Ysbyty Gwynedd 0248–370007 Llandudno General Hospital 0492–860066 Ysbyty Dewi Sant 0248–37036	8	1	6*

Health District and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Clwyd			
Wrexham Maelor General Hospital 0978–291100	9	1	8*
Ysbyty Glan Clwyd 0745–583910 (Fax 0745–583143)	8	—	7*
South Glamorgan			
University Hospital of Wales, Cardiff and associated hospitals† 0222–743107/743255 (Fax 0222–747203)	25	13	31
West Glamorgan			
Singleton Hospital, Swansea 0792–205666 (Fax 0792–208647) Morriston Hospital, Swansea 0792–702222 (Fax 0792–703632)	15	2	23*
Neath General Hospital 0639–641161 Port Talbot General Hospital 0639–641161	6	—	6*
Mid-Glamorgan			
East Glamorgan Hospital 0443–204242	7	—	4
Aberdare Hospital 0685–872411 Prince Charles Hospital, Merthyr Tydfil 0685–721721	6	—	4*
Princess of Wales Hospital, Bridgend 0656–662166 Bridgend General Hospital 0656–662166 Maesteg General Hospital 0656–732732	7	1	5*
Dyfed			
Bronglais Hospital, Aberystwyth 0970–623131	6	—	—
Prince Philip Hospital, Llanelli	4	—	3*
West Wales General Hospital, Carmarthen 0267–235151 (Fax 0267–237662)	6	—	4*
Pembrokeshire			
Withybush General Hospital, Haverfordwest 0437–764545	5	—	5*
Gwent			
Nevill Hall Hospital, Abergavenny 0873–852091 (Fax 0873–859168)	6	—	4
Royal Gwent Hospital, Newport and associated hospitals 0633–252244 (ext. 4590)	12	1	11*

*One or more posts rotate with Cardiff. †Associated with University of Wales College of Medicine.

Regional Educational Adviser:

Dr J. N. Horton, Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW. Tel. 0222–743107; Fax 0222–747203.

SOUTH EAST SCOTLAND

Hospital	Consultants	Senior registrars	Registrars/ SHOs
Edinburgh			
Royal Infirmary and associated hospitals 031–229 2477 (Fax 031–229 3337)	21+2 Hon(+5 P/T)*	6†(+2 Hon)*	15†/6
City Hospital 031–447 1001 (Fax 031–452 8363)	8 P/T*	1†	2†
Royal Hospital for Sick Children 031–667 1991 (Fax 031–662 4864)	4	1†	—/3†
Princess Margaret Rose Orthopaedic Hospital 031–445 4123 (Fax 031–445 3440)	14 P/T*	—	2†/1
Western General Hospital 031–332 2525 (Fax 031–332 7728)	11(+4 P/T)*	3†(1 P/T)*	4†/5
Eastern General Hospital 031–554 4444 (Fax 031–555 5118)	3(+1 P/T)	—	2†/1†

Hospital	Consultants	Senior registrars	Registrars/ SHOs
West Lothian			
St John's of Howden, Livingston 0506–419666 (Fax 0506–416484)	8	1†	2†/4
Borders			
General Hospital, Melrose 0896–4333 (Fax 0896–823476)	5	—	3(1†)
East Fife			
Victoria Hospital, Kirkcaldy and associated hospitals 0592–261155 (Fax 0592–202248)	8	—	4(2†)/3(1†)
West Fife			
Dunfermline and West Fife and associated hospitals 0383–737777 (Fax 0383–741056)	8	—	—/3(1†)

*Associated with Edinburgh University. †On rotation.

Regional Educational Adviser:
Dr I. T. Davie, Department of Anaesthesia, Western General Hospital, Crewe Road, Edinburgh EH4 2XU. Tel. 031–332 2525; Fax 031–332 7728.

GRAMPIAN, ORKNEY AND SHETLAND REGION

Hospital	Consultants	Senior registrars	Registrars/ SHOs
Aberdeen Royal Infirmary 0224–681818 Woodend General Hospital 0224–681818 Royal Aberdeen Children's Hospital 0224–681818 Aberdeen Maternity Hospital 0224–681818	23(+3 P/T)	7	10/13
Dr Gray's Hospital 0343–543131	2	—	—

Regional Educational Adviser:
Dr J. D. MacKenzie, Department of Anaesthesia, Aberdeen Royal Infirmary, Forest Hill, Aberdeen AB9 2ZD. Tel. 0224–681818; Fax 0224–685307.

SCOTLAND: HIGHLAND AREA

Hospital	Consultants	Senior registrars	Registrars/ SHOs
Raigmore Hospital, Inverness 0463–234151	7 (+1 P/T)	1†	3†

Regional Educational Adviser:
Dr J. H. Spenceley, Anaesthetic Department, Raigmore Hospital, Inverness IV2 3UJ. Tel. 0463–704000; Fax 0463–711322.

TAYSIDE REGION

Hospital	Consultants	Senior registrars	Registrars/ SHOs
Tayside			
Ninewells and Associated Hospitals 0382–60111	21 (+1 P/T) (includes 3 North Angus consultants)	6	16
Perth Royal Infirmary 0738-23311	5	—	6

†On rotation.

Regional Educational Adviser:
Dr N. Mackenzie, Department of Anaesthesia, Ninewells Hospital, Dundee. Tel. 0382–60111 (ext. 2175).

WEST OF SCOTLAND

Hospital	Consultants	Senior registrars	Registrars/ SHOs
Argyll & Clyde Health Board			
Inverclyde Royal Infirmary, Greenock 0475–33777 (Fax 0475–37340)	5	—	3
Royal Alexandra Hospital 041–887 9111 (Fax 041–887 6701)	8	—	4
Vale of Leven, Alexandria 0389–54121 (Fax 0389–55948)	4	—	2
Ayrshire & Arran Health Board			
Ayr County Hospital 0292–281991 (Fax 0563–39789)	19	—	10
Crosshouse Hospital 0563–21133 (Fax 0563–39789)			
Dumfries & Galloway Health Board			
Dumfries & Galloway Royal Infirmary 0387–53121 (Fax 0387–41639)	6	—	4
Forth Valley Health Board			
Falkirk Royal Infirmary 0324–24000 (Fax 0324–612340)	6	—	4
Stirling Royal Infirmary 0786–73151 (Fax 0786–50588)	7	—	3
Greater Glasgow Health Board			
Royal Infirmary* 041–552 3535 (Fax 041–304 4889)	24	10	24
Southern General Hospital 041–445 2466 (Fax 041–445 3670)	11	—	11
Stobhill General Hospital 041–558 0111 (Fax 041–557 0468)	10	—	11
Victoria Infirmary 041–649 4545 (Fax 041–649 2206)	14	5	17
Western Infirmary* 041–339 8822 (Fax 041–339 2628)	28	9	22
Lanarkshire Health Board			
Law Hospital 0555–351100	10	—	8
Monklands District Hospital 0236–69344 (Fax 0236–755480)	9	—	10
Hairmyres Hospital 03552–20292	7	—	4
Specialist Hospitals			
Institute of Neurological Sciences, Glasgow 041–445 2466 (Fax 041–425 1583)	6	1§	4§
Royal Hospital for Sick Children, Glasgow 041–339 8888 (Fax 041–334 0972)	10	2§	5§

*Associated with university departments. §On rotation.

Regional Educational Adviser:
Dr J. P. Vance, Department of Anaesthesia, Royal Infirmary, Glasgow G4 0SF. Tel. 041–552 3535.

NORTHERN IRELAND

Board and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Eastern			
Royal Victoria Hospital 0232–240503	29	8	2/8
Belfast City Hospital 0232–329241	20	4	2/7
Ulster Hospital 0232–484511	9	2	2/3
Queens University, Belfast (Department of Anaesthetics) 0232–245133	3	3	2/—
Lagan Valley Hospital 0846–665141	2	—	1†/—
Mater Infirmorum 0232–741211	3*	—	1††/1
Western			
Altnagelvin Area Hospital 0504–45171	6	1	3/3
Southern			
Craigavon Hospital 0762–334444	7	1	2/2
Daisy Hill Hospital 0693–65511	4	—	1/1

Board and Hospital	Consultants	Senior registrars	Registrars/ SHOs
Northern			
Waveney Hospital 0266–652534	3	1	2/1
Coleraine Hospital 0265–44177	3	—	1/1
Whiteabbey Hospital 0232–865181	2	—	—/1†††

N.I. Junior Staff from 1 August 1991.
*Two consultants sharing one post.
On rotation with, †Belfast City Hospital, ††Royal Victoria Hospital, †††Waveney Hospital.

Regional Educational Adviser:
Dr I. W. Carson, Department of Anaesthetics, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA. Tel. 0232–240503 (ex. 4006).

Royal College of Anaesthetists Guide to Training

Including guide to the Examinations for the Diploma of Fellow of the Royal College of Anaesthetists (F.R.C.Anaes.) and Diploma in Anaesthetics (United Kingdom) (D.A. (U.K.))

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USEFUL ADDRESSES AND TELEPHONE NUMBERS

Royal College of Anaesthetists
48–49 Russell Square, London WC1B 4JP
Tel. 071-813 1900. Fax 071-813 1876.
071-813 1880 (Examinations Department);
071-813 1888 (Education Department);
071-637 1162 (Finance Department).

Enquiries
Overseas Doctors Training Scheme: Ext. 109
Bernard Johnson Careers Adviser: Ext. 109

For EC doctors (EC Nationals holding EC qualifications) enquiring about Registration and about limited Registration and the PLAB test:
The Registrar
General Medical Council
44 Hallam Street
London W1N 6AE: 071-580 7642

For enquiries about residential accommodation:
Nuffield College of Surgical Sciences,
34–43 Lincoln's Inn Fields, London WC2A 3PN.
Tel. 071-405 3474 (Ext. 2000).

For enquiries about medical practice insurance:
Medical Defence Union
3 Devonshire Place
London W1N 2AE: 071-486 6181
Medical Protection Society
50 Hallam Street
London W1N 6DE: 071-637 0541
Medical and Dental Defence Union of Scotland
144 West George Street
Glasgow G2 2HW: 041-332 6646

INTRODUCTION

The Royal College of Anaesthetists supervises the training of anaesthetists throughout the United Kingdom and helps with training in other parts of the world. It awards two qualifications in anaesthesia by examination—a Diploma and a Fellowship. In addition, it plays a leading role in the work of the Joint Committee for Higher Training of Anaesthetists which accredits Fellows who have undergone the necessary post-Fellowship training as being prepared for appointment to the Consultant grade in the National Health Service within the United Kingdom.

This section is designed to explain the training system and to set out the relevant regulations for the examinations and for final accreditation.

The regulations for the F.R.C.Anaes. diploma (the last part of this section) set out the conditions with which the trainee must comply before being eligible to sit each part of the examination. Before the trainee embarks upon courses of study or clinical training it is strongly advised that he finds out the training and experience needed in order to comply with these regulations.

Enquiries about the Regulations and individual eligibility should be addressed in writing to the Examinations Department and accompanied by a full curriculum vitae (including the college or university at which a medical degree was obtained, details of experience since graduation and the names and addresses of the hospitals at which the trainee has worked, with dates).

General enquiries concerning training should be addressed to the Secretary of the College.

1. HISTORY

The first examination in anaesthesia (a Diploma in Anaesthetics) was instituted jointly by the Royal Colleges of Surgeons and Physicians in London on the prompting of the Association of Anaesthetists of Great Britain and Ireland and the Anaesthetic Section of the Royal Society of Medicine. It was first held in 1935. In 1948 the Faculty of Anaesthetists in the Royal College of Surgeons of England was founded and instituted the Fellowship examination (the F.F.A.R.C.S.). Similar Faculties (and examinations) were created by the Surgical Colleges in other countries.

In 1988, by Royal Charter, the Faculty of Anaesthetists became the College of Anaesthetists. It was established as a College within the Royal College of Surgeons of England. In 1992, the College was granted a Royal Charter and moved to its own premises at Russell Square. The name of the Fellowship was changed to the Fellowship of the Royal College of Anaesthetists (the F.R.C.Anaes.). [All Fellows of the Faculty automatically became Fellows of the new College. Those who obtained the F.F.A.R.C.S. before 1989 are entitled to use either F.F.A.R.C.S. or F.R.C.Anaes. as they wish although the latter is the more correct form. Those who obtained a Fellowship later than 1988 may only use F.R.C.Anaes.]

2. CAREERS IN ANAESTHESIA

Training in anaesthesia falls into two parts. An initial period of *Basic Specialist Training* ends usually shortly after gaining the F.R.C.Anaes. diploma. Subsequently there is a period of *Higher Specialist Training* which leads to accreditation and to being eligible for appointment to a consultant post. Careers advice can be obtained from the Bernard Johnson Adviser at the College.

Basic Specialist Training

The regulations for the Fellowship examination demand that the trainee has spent at least four years since qualification in medicine and that of these four years the first must be spent in pre-registration house officer posts (or their equivalent) and two of the other three must be in recognized anaesthetic posts. Of these two anaesthetic years one must be spent in a hospital approved under Schedule I* within the United Kingdom. Schedule I hospitals provide a full range of basic anaesthetic services together with some more specialized work. Schedule II* hospitals which may be involved with the other year of training either cannot provide the necessary broad base of experience needed or provide only very specialized services. Recognized rotational training schemes are being encouraged by the College. The College makes no specific demands as to how the fourth year of training should be spent: the trainee may work in anaesthesia or in other disciplines. The College recommends that anaesthetists should broaden their general experience by working in other acute hospital specialities but realizes that this may not always be possible. The regulations are written to embrace all candidates including those from overseas who may have only limited registration with the General Medical Council.

The first year of anaesthetic training is normally spent in the senior house officer grade or its equivalent. By the end of that year the trainee should have sufficient knowledge and experience to pass the Part 1 of the College's Fellowship examination. This Part tests the knowledge needed to practise independently for most types of routine and some emergency anaesthesia. Passing the Part 1 examination and completing 12 months' satisfactory training in a recognized post confers eligibility for the award of the Diploma in Anaesthetics of the College. If the trainee at this stage wishes to leave anaesthesia, for example to work in general practice, the possession of the Diploma is a mark of suitability to undertake some limited anaesthetic practice, perhaps as a clinical assistant.

The subsequent years of basic training exposes the trainee to a wide variety of anaesthetic work including intensive care and the anaesthetic aspects of obstetrics. In addition, the trainee may well see work in the specialties of thoracic, cardiac, paediatric and neuroanaesthesia and chronic pain relief. The Part 2 examination is a basic test of the physiological and pharmacological background to anaesthesia and is usually taken within a few months of the Part 1. The Part 3 examination is usually taken towards the end of or just after the completion of the four year training period.

Higher Specialist Training

After passing Part 3 and gaining the Fellowship, the trainee is regarded as eligible for appointment to a senior registrar post (or its equivalent in universities). Before accreditation by the Joint Committee for Higher Training of Anaesthetists (JCHTA), the trainee will need to spend at least three further years in anaesthesia. Of these, two must be spent in an approved senior registrar post and one must be spent in a teaching hospital. The JCHTA will approve up to a maximum of one year for any time spent in other posts in either the United Kingdom, the Republic of Ireland or overseas, and will also accept that the third year may be spent in full-time research. It is important that the third year be spent in a post where the work is supervised. The supervision of Higher Specialist Training is under the aegis of the Joint Committee for Higher Training of Anaesthetists. This body comprises representatives from the College, the Irish Faculty, the Association of Anaesthetists and the Association of Professors in Anaesthesia.

Thus the minimum time before the College would regard any trainee as being eligible for appointment as a consultant within the NHS is seven years following qualification at medical school. Of the initial four years, two must be spent in a recognized post in anaesthesia and one of these must be spent in a Schedule I post in the United Kingdom. Of the final three years, two must be spent in substantive posts in the senior registrar grade and one of these must be spent in a teaching hospital.

3. SUPERVISION OF TRAINING

The College works in two ways to supervise the training of anaesthetists. First, it inspects all the hospitals involved with both basic and higher specialist training to ensure that the facilities are adequate, that they are well equipped, that the experience available is appropriate and that the teachers are both willing and able to teach. Both types of training are inspected at five year intervals or more frequently should that be needed.

Second, the College appoints in each region of the NHS a Regional Educational Adviser with the assistance of one or more deputies. In each district it appoints a College Tutor. The aim is that the Tutors will ensure that there is proper training in each district and that together with the other Tutors and the Educational Advisers, comprehensive plans for the more formal aspects of training can be achieved in each region or obtained by secondment to national courses where appropriate.

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*A list of Schedule I and Schedule II posts is available from the Examinations Department.

4. GMC REGULATIONS

Full registration is granted to those whose undergraduate training, final graduation examinations and first year of clinical experience have been inspected and approved by the General Medical Council. Qualifications currently recognized by the GMC as acceptable for full registration are listed in Appendix 1.

Graduates of most other universities can only obtain limited registration. To obtain limited registration the trainee must pass, unless exempted (as will often be the case if sponsored under the Overseas Doctors Training Scheme), the test of the Professional and Linguistic Assessments Board (PLAB) of the General Medical Council (See Appendix 2).

The trainee cannot be appointed as a senior house officer or a registrar in the United Kingdom until he has been granted full or limited registration.

5. RECOGNIZED HOSPITAL APPOINTMENTS

(a) United Kingdom

A list of the hospital posts in the United Kingdom recognized by the College is available on request from the Examinations Department. Trainees from overseas should be aware that they may experience difficulty in securing recognized hospital appointments in the U.K., because of intense competition for the available posts.

Appointments are advertised in the medical journals and application should be made to the employing authority as indicated in the advertisement. Selected applicants are placed on a short list, following which they will be called for interview by the employing authority.

The College can help in obtaining recognized hospital appointments through the Bernard Johnson Adviser or Overseas Doctors Training Scheme. Under this scheme approved sponsors, not the trainees, initiate recommendations to the College.

Experience acquired in full-time supernumerary (unpaid) appointments at recognized hospitals in the U.K. is capable of being accepted for recognition for named individuals by agreement between the College and hospitals concerned. The College must be satisfied that the duties are identical with those of a recognized full-time paid post, and are completed under full or limited registration.

Part-time training may also be accepted with the prior approval of Council.

(b) Overseas

Apart from the hospitals listed under regulation 2.3 (note 2) overseas posts are not recognized by the Council.

The Credentials Committee of the College is prepared to assess training in non-recognized posts overseas and may allow a maximum of one year of such training to count towards Schedule II training but only if the other year is spent in a Schedule I post in the U.K. Applications should be made four weeks before the closing date.

The College tries to be as flexible and liberal as possible in assessing the suitability of training. If in doubt write to the Examinations Secretary.

6. THE EXAMINATIONS CALENDAR

The dates of forthcoming examinations are published annually in the Examinations Calendar. The calendar also contains full details of the examination and diploma fees and the method of payment. It may be obtained from the Examinations Department.

There are three sittings each year of the Parts 1 and 2 examinations. The Part 3 examination is held twice each year.

If candidate numbers justify, the Parts 1 and 2 examinations are also held in Cairo.

The written papers may be sat in Scotland or Manchester at the same time as the London sitting.

7. LOG BOOKS

The trainee is required to keep a log book recording anaesthetic experience.

8. COURSES AVAILABLE IN PREPARATION FOR THE F.R.C.Anaes.

Details of the courses organized by the Royal College of Anaesthetists can be obtained from the College Office.

Many university departments and postgraduate centres run courses in preparation for the examination, though it should be possible to obtain adequate teaching for the Part 1 examination in any hospital recognized by the College. Courses are usually advertised in the anaesthetic journals. To gain the maximum benefit from such courses one must have a fluent command of the English language.

9. QUESTION PAPERS

Past examination papers (other than multiple-choice question papers) are published annually and may be obtained on application to Adrian Press Ltd., Dept. E.4, 60 Oaklands Park Avenue, Ilford, Essex IG1 1TG, at the price quoted in the annual Examinations Calendar.

10. RESIDENTIAL ACCOMMODATION WITHIN THE ROYAL COLLEGE OF SURGEONS

A limited amount of residential accommodation for students attending courses is available at the Nuffield College of Surgical Sciences. Details may be obtained from the Residence Officer.

GUIDE TO THE GOALS AND CONTENT OF THE EXAMINATION

INTRODUCTION

The F.R.C.Anaes. examination is designed to test knowledge and ability to apply that knowledge in the broad fields of anaesthesia, intensive therapy and pain relief covered during BST. A knowledge of the principles of the specialized areas of HST is required, but not the details of practice in these areas.

The examination comprises three parts:

- —The first part tests the fundamentals of clinical practice.
- —The second part tests the applied basic sciences relevant to anaesthesia.
- —The third part tests ability to apply the knowledge gained in working for the first and second parts to the clinical experience outlined above.

Although no syllabus is issued for any part of the examination, the following outline covers the main areas of knowledge and experience with which the trainee is expected to be familiar.

THE PART 1 EXAMINATION

Level of experience

Although no recognized anaesthetic training is required for entry to the Part 1, the examination aims at an assessment of competence appropriate for the trainee at the end of the first year of anaesthesia.

A. Goals of the examination

1. To demonstrate knowledge of how to administer a general or local anaesthetic to a fit adult patient for a straightforward elective inpatient or outpatient surgical procedure and to provide appropriate postoperative pain relief.
2. To demonstrate knowledge of the principles of care of children (excluding neonates) undergoing anaesthesia for straightforward surgical procedures including ENT, eye and dental surgery.
3. To demonstrate knowledge of immediate care and resuscitation in patients of all ages to the level of advanced cardiopulmonary resuscitation (CPR).
4. To demonstrate knowledge required to deal with emergencies before, during and after anaesthesia, and the ability to stabilize a patient's condition until senior assistance can be obtained.
5. To demonstrate a knowledge of the principles of obstetric analgesia and anaesthesia.

B. Main areas covered in the examination

1. *Commonly used anaesthetic equipment and techniques:*
Physical principles underlying the function of anaesthetic machines and delivery systems. Methods of checking their performance in clinical practice. Related anaesthetic equipment, together with equipment used for local anaesthesia and resuscitation. Complications occurring during anaesthesia and the recovery period. Basic techniques for administering general anaesthesia. The principles of patient monitoring of anaesthetized and unconscious patients, and the recording of relevant data. Accuracy and limitations of patient monitoring equipment.

2. *Preoperative assessment:*
Preoperative assessment of a patient of any age (excluding neonates) for elective or emergency surgery including relevant investigations. Preparation of patients for anaesthesia, including fluid administration. Understanding of the commoner medical diseases and surgical disorders and their implications for anaesthesia. Ability to discern when more senior anaesthetic help will be required.

3. *Applied basic sciences:*
Knowledge of the relevant anatomy, physiology and pharmacology to allow an effective choice of technique for the patients listed under **A**, above, including:

(i) Anatomical knowledge relevant to general and local anaesthesia, including knowledge of upper limb, intercostal and field blocks and the principles of spinal and extradural techniques with their complications.
(ii) Basic physiological principles together with an understanding of the physiological effects of commonly used anaesthetic agents and techniques.
(iii) The pharmacology of drugs commonly encountered in anaesthetic practice, together with their dosage, side effects and interactions with other drugs.

4. *Care of the patient recovering from anaesthesia* and of the unconscious patient in the accident and emergency department or other environment.

5. *Resuscitation* of patients with airway problems, ventilation problems, hypovolaemia, circulatory failure or cardiac arrest.

THE D.A. (U.K.)

Candidates who have passed the F.R.C.Anaes. Part 1 and satisfactorily completed one year in approved Schedule I or II posts in the *United Kingdom* may apply for the award of the Diploma of D.A. (U.K.), which must be claimed within three years of passing Part 1. (Candidates applying after three years of passing Part 1 will be charged an additional fee.)

THE PART 2 EXAMINATION

A. Goals of the examination

Successful candidates will have achieved a detailed knowledge and advanced level of understanding of the basic component subjects. The attainment of such a standard in the basic sciences of anaesthetic practice will permit progress to the Part 3 examination, but more importantly will provide a scientific basis for clinical practice as it develops and changes over a career in anaesthesia.

B. Main areas covered in the examination

1. *Pharmacology*
The general properties of molecules, and the nature of chemical reactions. The physicochemical properties of drugs and their formulations. Pharmacokinetics, pharmacodynamics and drug receptor interactions. Variability of individual responses to drugs. Adverse reactions to drugs, including drug interactions. Drug delivery systems. The systematic pharmacology of drugs used in anaesthesia and intensive therapy. Some knowledge of unrelated drugs which may be part of current therapy when patients present for anaesthesia.

Basic statistics. The principles by which experimental data may be collated, summarized and plotted. Commonly used population distribution curves. Parametric and non-parametric tests of statistical significance, and the principles of experimental design, including estimation of the power of a study. Confidence limits.

2. *Physiology*
The basic principles of human physiological processes, with special emphasis on the nervous, cardiovascular and respiratory systems. The clinical application of physiological principles, with particular reference to controlled ventilation of the lungs, anaesthesia and intensive therapy.

The measurement of important physiological variables, and the physical principles involved. There will be special emphasis on those measurements which are used in anaesthesia and intensive therapy for the assessment of neurological, cardiac, respiratory, renal and hepatic function.

THE PART 3 EXAMINATION

Level of experience

Candidates will be expected to be approaching the end of Basic Specialist Training (BST). The experience gained will have included not only the administration of anaesthesia for most types of surgery but also wide experience in the obstetric and intensive therapy units. The trainee will also be expected to have received training in the principles of those specialist subjects encountered in Higher Specialist Training (HST) such as anaesthesia for cardiac, thoracic, paediatric (including neonatal) and neurosurgery and in the management of patients needing relief from chronic pain; though the trainee may not have had practical experience in these areas.

A. Goals of the examination

In the light of experience obtained during BST, to demonstrate the ability to apply the knowledge gained in studying for the Part 1 and 2 examinations, together with regular study of easily available anaesthetic literature, to clinical situations. These will include preoperative assessment and preparation, anaesthetic management, early postoperative care and pain relief, management of patients in need of intensive therapy and all aspects of resuscitation.

B. Main areas covered by the examination

1. *Acute medicine and surgery*
Aspects of medicine and surgery related to pre-, intra- and postoperative care and intensive therapy, including drug intoxication and other medical and surgical emergencies.

2. *Preoperative preparation : assessment*
History, relevant clinical examination and investigations. Clinical implications of the effects of anaesthesia and surgery on the patient. Anaesthetic implications of age, nutritional and metabolic state, personal habits (e.g. smoking, drug addiction), surgical condition and drug therapy.

Preoperative preparation : preparation of patient
Routine preparation of patients of any age for surgery. Preoperative medication. Special considerations for day-case surgery, specific types of surgery, obstetrics and emergency surgery.

3. *General anaesthesia*
Mechanisms of anaesthesia and analgesia. Methods of administration. Pharmacology of drugs used in anaesthetic practice, choice of appropriate drugs and techniques in specific situations.

Physiological and pharmacological effects of anaesthesia. Anatomy relevant to anaesthetic practice. Complications of anaesthesia. Mechanisms of muscle relaxation and pharmacology of muscle relaxants, indications for their use, complications. Clinical measurement relevant to anaesthesia and intensive therapy. Indications, use, limitations and hazards of equipment used in anaesthesia, including monitoring equipment. Sources of error and interpretation of data.

Patient care during anaesthesia and surgery. Specific problems associated with and detailed anaesthetic management of surgical procedures normally seen during BST, including obstetric anaesthesia.

General principles of anaesthetic management of surgical procedures normally seen during HST.

Special techniques associated with anaesthesia such as induced hypotension and hypothermia, intraoperative pain relief, morbidity and mortality.

4. *Local anaesthesia*
Anatomy and physiology relevant to surface, infiltration and local anaesthesia. Equipment, techniques, indications, effects and complications. Pharmacology of local anaesthetic agents. Toxicity. Morbidity and mortality.

5. *Postoperative care*
Postoperative assessment and monitoring. Aetiology, symptoms, signs, effects and management of complications occurring in the immediate postoperative period. Late postoperative complications. Care of the unconscious patient. Postoperative pain relief. Specific postoperative problems related to special types of surgery and anaesthetic techniques.

6. *Intensive therapy*
Physiology of major systems. Pathophysiology of organ system failure. Diagnostic invasive and non-invasive procedures. Investigation and management of patients, including respiratory care, fluid balance, sedation and analgesia. Monitoring. Organ support, pharmacology, physiology, technology.

Resuscitation and immediate care (see below). Management of trauma (see below). Management of specific diseases requiring intensive therapy. Nutrition. Infection control and sterilization of equipment. Complications of intensive therapy. Morbidity and mortality. Severity scoring. Audit. Ethics. Brain stem death. Organ transplantation. Hazards of electrical and other equipment.

7. *Cardiopulmonary resuscitation and immediate care*
Aetiology, assessment and immediate management of cardiac and respiratory arrest in patients of all ages. Life-threatening disorders of cardiac rhythm. Emergency cardiac pacing. Resuscitation algorithms. Principles, initial assessment and immediate management of trauma life support. Transport of gravely ill patients. Preparation for mass emergencies. Ethical considerations.

8. *Scientific aspects of anaesthesia and intensive therapy*
Relevant innovations and developments in anaesthesia, intensive therapy and pain relief reported in the medical literature. Critical assessment of scientific publications. Design of clinical trials and interpretation of data. The application of computers to anaesthetic practice. Clinical audit.

9. *Management of trauma*
Principles, initial assessment and immediate management. Triage. Identification and immediate treatment of life-threatening injuries. Airway management and artificial ventilation. Hypovolaemic, cardiogenic and neurogenic shock. Neurological assessment. Management of head, maxillofacial, spinal, cardiothoracic, vascular and other major injuries. Assessment and management of burns. Complications of therapy.

10. *History of anaesthesia*
Whilst candidates are unlikely to fail the examination because of a lack of knowledge of the historical development of anaesthesia, the acquisition of such knowledge is encouraged.

THE FORMAT OF THE EXAMINATION

GENERAL INFORMATION ON METHODS OF ASSESSMENT

The College uses combinations of multiple choice question papers (MCQ), written answer papers, clinical and oral elements in its examinations. MCQs are marked by computer and all other elements are marked by pairs of examiners working independently. No pair of examiners marks more than one element for any individual candidate, nor are they aware of the marks awarded by any other pairs of examiners for any candidate until that candidate's examination is completed.

MCQ

The principal function of this is to test the adequacy of recall of factual knowledge. The type of question used is the same throughout the examination and consists of a stem and five completions, each of which in conjunction with the stem is either a true or a false statement. The trainee may state for each response whether it is true or false or may choose not to answer. Candidates receive +1 mark for each correctly answered response, −1 for each response incorrectly answered and 0 if no attempt is made to answer. A "don't know" box is included on the answer sheet.

At each examination the trainee receives a question book detailing the questions and a printed answer sheet on which to mark the answers. The trainee is not allowed to retain the question book. The trainee is advised, in the examination instructions, to enter answers in the question book first and then to transpose them to the answer sheet.

Written answer paper

Unlike the MCQ, the written answer papers are designed not only to test accurate recall of facts but also to give an indication of ability to select the most relevant pieces of information, to assign relative importance to each and to assemble them logically. Tabulated telegraphic answers in which all the correct information is randomly located within material that is of doubtful relevance are not necessarily, therefore, of a pass standard.

Written answers are also a test of ability to communicate clearly and unambiguously and thus legibility and a reasonable command of the English language are relevant.

With the use of the close-marking system, failure to attempt the required number of questions will result in failure to pass the examination.

Oral examinations

Oral examinations provide a profile of knowledge over a broader range of topics than can be tested by the written answer paper, and in greater depth than the MCQ. They also allow the trainee to demonstrate the ability to apply factual knowledge to clinical situations, to demonstrate sound judgement with emphasis on the most important aspects of any topic, to solve problems posed by the examiners and to justify the answers given.

Clinical examinations

The College regards the test of medical knowledge as one of the most important aspects of the Fellowship examination. Clinicals are held in the Part 1 (without patients) and in the Part 3 (with patients).

Part 1

In the Part 1 there is a 30-minute clinical oral with two examiners. This is preceded by a 10-minute period during which candidates study some written information concerning a hypothetical patient together with the results of relevant investigations. There are also other clinical problems related to visual material such as x-rays, ECGs, biochemical or haematological results. All candidates who are simultaneously being examined will receive the same material and broadly similar questioning.

Part 3

In the Part 3 there is a 55-minute clinical examination beginning with 25 minutes for history-taking and examination of a patient. This is followed by an oral examination with two examiners in which emphasis is placed on the candidates' ability to elicit the key points in the history and to conduct an appropriate clinical examination. Approximately half of the 30-minute oral is devoted to discussion of the clinical case and the second half is then spent in discussion of x-rays, ECGs and other clinical material unrelated to the patient with whom the trainee has spent the first 25 minutes. The Part 3 clinical will take the format of an Objective Structured Clinical Examination (OSCE) from June/July 1994. (Further details can be obtained from the Examinations Department.)

STRUCTURE OF THE EXAMINATIONS

Part 1

There are four sections:

(a) 60 multiple choice questions — 2 hours.

(b) Seven compulsory written answers —3 hours.

(c) Clinical oral using guided questions (see above) — 25 minutes.

(d) Oral with two examiners, approximately half of which is devoted to the physical principles underlying the working and safe use of commonly used anaesthetic and monitoring apparatus — 30 minutes.

Part 2

There are four sections:

80 multiple choice questions comprising, (a) 40 in pharmacology and, (b) 40 in physiology — 2 hours 40 minutes. (c) Pharmacology oral — 20 minutes. (d) Physiology oral — 20 minutes. Each oral is with two examiners.

Part 3

There are five sections:

(a) Written answer paper — 3 hours. There are eight questions in two groups of four. The trainee must answer a total of five questions, choosing two from each group and the fifth from either group. The subject matter covers all aspects of anaesthetic practice including intensive therapy and acute pain relief, apparatus, clinical measurement and relevant applied physiology, pharmacology and anatomy.

(b) 90 multiple choice questions covering the same subject matter as the written answer paper, together with questions in medicine and surgery.

(c) Clinical examination with patient — 55 minutes (see above).

(d) Two oral examinations, each with two different examiners — 30 minutes each.

THE MARKING SYSTEM

The College uses a 4-point close-marking system in all its examinations, the marks used being:

2+ (good pass)
2 (pass)
1+ (fail by a small margin)
1 (bad fail)

The following marks are required to pass each part of the examination:

Part 1: 2, 2, 2, 1+ or better
Part 2: 2, 2, 2, 1+ or better
Part 3: 2, 2, 2, 2, 1+ or better

In all parts of the examination the performance of borderline candidates is reviewed by all the examiners before the final marks are awarded.

REGULATIONS

1. ELIGIBILITY

Fellowship of the Royal College of Anaesthetists (F.R.C.Anaes.)

1.1 The Diploma of Fellow of the Royal College of Anaesthetists and the Diploma in Anaesthetics of the United Kingdom may be granted to those who possess a qualification fully registrable in the British Medical Register, or to those who are *eligible* for limited registration in the United Kingdom who have complied with the regulations that follow and have passed the required examinations.

1.2 Candidates for the Diploma of Fellow are required to pass three examinations in succession, namely Parts 1, 2 and 3.

1.3 The Diploma of Fellow of the College will not be granted to a candidate who has not attained 25 years of age. A candidate may, however, enter for the Part 3 examination before this age has been reached.

Diploma in Anaesthetics (United Kingdom) (D.A. (U.K.))

Candidates who have passed Part 1 and satisfactorily completed one year in approved Schedule I or II posts in the United Kingdom, may apply for the award of the Diploma, which must be claimed within three years of passing Part 1 or an additional charge is made.

The Diploma replaced the D.A. (England) from February 1985. The new Diploma entitles the holder to the same status and seniority as did its predecessors, the D.A. (England) and the D.A., R.C.P. London and R.C.S.

England. Holders of these Diplomas may not apply for the D.A. (U.K.).

2. ENTRY REQUIREMENTS

Part 1

2.1 (a) Candidates are admissible to the Part 1 examination after obtaining one of the qualifications specified in regulation 1 except that:

(b) Candidates holding qualifications fully registrable in this country may not be admitted to the examination until they have completed satisfactorily the 12 months' period of service in approved pre-registration appointments as required by the Medical Act 1983.

(c) Candidates holding qualifications which are not fully registrable in this country must produce evidence that they have completed not less than one year's clinical experience after qualification so that they may hold, or be eligible to hold, limited registration in accordance with regulation 1. This experience must include at least nine months in clinical posts other than in anaesthesia, and should preferably include six months in a medical post.

The reference to limited registration is intended to ensure that candidates from overseas are likely to be able to complete the clinical training required before award of the D.A. (U.K.) or entry to the Part 3 examination. Those not eligible for full registration must expect to complete their training in the United Kingdom under limited registration normally after success in the PLAB Test of the General Medical Council (address for enquiries: 153 Cleveland Street, London W1P 6DE).

Specific periods of anaesthetic training in posts approved by the College are not required for entry to Part 1, but the guidelines presuppose about one year of anaesthetic experience and study under supervision.

Part 2

2.2 Candidates are admissible to the Part 2 examination after passing Part 1 (but see regulations 3.1 and 3.2 for exemptions).

Part 3

2.3 Candidates who have passed the Part 1 and Part 2 examinations described above, and those who are exempt therefrom (see regulations 3.1 and 3.2 below), and have completed not less than four years since obtaining a qualification specified in regulation 1.1, may enter for the Part 3 examination when they have:

(a) held clinical house appointments, other than in anaesthetics, for at least* 12 months in posts that make them eligible for full or limited registration in the United Kingdom;

(b) completed not less than two years of full-time training in a post or posts approved by, or acceptable to, the College for this purpose, of which at least one year (12 months) should normally have been spent in a post or posts in the United Kingdom included in the list of Schedule I posts available from the Examinations Department. Those not eligible for Full Registration must expect to complete their training in the United Kingdom under limited registration, normally after success in the PLAB Test of the General Medical Council.

Notes:

1. Candidates who wish to present a claim that they have had or intend to complete equivalent experience in the United Kingdom or overseas (e.g. in the Republic of Ireland) that might exempt them from the requirement to complete 12 months in Schedule II posts, shall submit their case to the Examinations Secretary for assessment by the Credentials Committee of the College.

2. To satisfy the requirements of regulation 2.3(b) candidates may offer, towards the two years' total requirements, up to 12 months' experience in: (i) a post or posts listed in the column headed Schedule II Posts in the list of approved posts; and/or (ii) a post or posts regarded as equivalent to Schedule II experience, viz:

(a) Teaching hospitals in the Commonwealth or former Commonwealth associated with universities whose degrees are fully registrable with the General Medical Council.

(b) Hospitals recognized by the Faculty of Anaesthetists in the Royal College of Surgeons in Ireland, the Royal Australasian College of Surgeons and the College of Medicine of South Africa, or by the American Board of Anesthesiology, or the Royal College of Physicians of Canada.

2.4 In the case of candidates whose Schedule II experience falls marginally short of any requirement, the Council of the College may allow admission at its discretion.

Requests must be received by the Examinations Department *at least four weeks* in advance of the closing date specified in the examinations calendar, but preferably earlier.

3. EXEMPTIONS

3.1 Exemption from Part 1 is allowed to holders of the European Diploma in Anaesthesiology and Intensive Care.

3.2 Exemptions from Parts 1 and 2 are allowed as follows:

(a) To those who have passed, in or before 1984, the Primary F.F.A.R.C.S., the Primary F.F.A.R.A.C.S. or the Primary F.F.A.C.M.S.A., or (in or before 1985) the Primary F.F.A.R.C.S.I.

(b) To those who hold the Fellowship in Anaesthetics of the Irish, Australasian, or South African Colleges, or the certificate of the American Board of Anesthesiology or the Fellowship in Anaesthesia of the Royal College of Physicians of Canada, or the M.D. (Anaesthesiology) of the University of Sri Lanka† (obtained in or after 1980), or the M.Med. (Anaesth.) of The University of Nairobi† (obtained in or after 1984), or the Mastership in Anaesthesia of the University of Khartoum† (obtained in or after 1989), the M.Med. (Anaesthesia) of the National University of Singapore* (obtained in or after 1991) or such other degrees or diplomas as the Council may from time to time accept.

(c) Success in the F.F.A. Parts 1 or 2 of the Irish College provides reciprocal exemption from the corresponding F.R.C.Anaes. Part 1 or 2 examination.

Those who claim exemption under (a), (b) or (c) but wish to seek award of the D.A. (U.K.) must, however, take and pass the Part 1 examination.

4. APPLICATION FOR ADMISSION

4.1 Applications for admission to an examination must reach the Examinations Department by the published closing date.

4.2 Applications for admission to an examination must be accompanied at first entry by the required certificates and the fee payable.

5. WITHDRAWALS

5.1 A candidate withdrawing an application for admission to an examination may receive back the full amount of the fee paid, provided that such withdrawal is received in writing before the closing date.

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*The Council of the College recommends but does not specifically require that, in addition to the above (normally pre-registration) experience, candidates should spend a further six months in a post of a medical nature.

†Subject to annual renewal of approval.

5.2 A candidate withdrawing an application for admission to an examination on or after the closing date, or who fails to appear for an examination for which an entry has been accepted, will not normally be entitled to any refund of fee.

6. FEES

6.1 The fees payable for admission to each Part are contained in the annual Examinations Calendar.

6.2 The additional fee payable before the Diploma of Fellow may be granted is shown in the Examinations Calendar. The additional fee for award of the D.A. (U.K.) is also shown in the Examinations Calendar.

6.3 An annual subscription is payable by every Fellow whose diploma is granted after 1 December 1957. The amount of the subscription is determined by the College and is payable annually on 1 April or 1 October, whichever follows next after the date on which the diploma is granted.

7. INFRINGEMENT OF THE REGULATIONS

7.1 The Council of the Royal College of Anaesthetists may refuse to admit to an examination, or to proceed with the examination of, any candidate who infringes any of the regulations, or who is considered by the examiners to be guilty of behaviour prejudicial to the proper management and conduct of the examination.

8. ELIMINATION AND REFERRAL

Part 1

8.1 Candidates whose performance in the multiple choice question paper of the Part 1 examination is very poor will be debarred from the oral examination except at overseas centres.

8.2 Counselling:

(i) After the fourth attempt at the Part 1 examination resulting in referral or elimination the candidate will not be allowed to enter for the examination again until: (a) A confidential report has been obtained from the candidate's College Tutor with the consent of the candidate; (b) The candidate has attended a counselling session at the College.

(ii) After the counselling session two further attempts will be permitted after which the candidate will not be allowed to proceed further in the F.R.C.Anaes. examination.

Part 2

8.3 Counselling:

After the fourth attempt at the Part 2 examination resulting in referral or elimination, the candidate will not be allowed to enter for the examination again until:

(i) A confidential report has been obtained, with the candidate's consent, from his/her College Tutor;

(ii) The candidate has attended a counselling session at the College.

Part 3

8.4 The written and MCQ papers in the Part 3 examination are eliminatory (except at overseas centres). Candidates who obtain a fail mark in both papers are debarred from the clinical examination.

8.5 More than one bad fail mark (1) will lead additionally to referral for 12 months (to include nine months in approved Schedule I posts in the United Kingdom).

8.6 Counselling:

After the fourth attempt at the Part 3 examination resulting in referral or elimination, the candidate will not be allowed to enter for the examination again until:

(i) A confidential report has been obtained, with the candidates consent, from his/her College Tutor;

(ii) The candidate has attended a counselling session at the College.

9. Representations

A candidate desiring to make representations with regard to the conduct of the examination must address them to the Examinations Secretary, and not in any circumstances to an examiner before the commencement of the subsequent examination.

APPENDIX 1

OVERSEAS QUALIFICATIONS RECOGNIZED BY THE GENERAL MEDICAL COUNCIL FOR FULL REGISTRATION

1. Registrable qualifications granted in member states of the European Community (EC) when held by a national of a member state of the EC.

2. The primary qualifications shown in the table below are recognized by the General Medical Council under section 19 of the Medical Act 1983 for the purpose of full

Country or state	Body granting qualifications	Primary qualifications
Australia		
New South Wales	University of Newcastle, NSW	B. Med.
	University of New South Wales	M.B. B.S.
	University of Sydney	M.B. B.S.
Queensland	University of Queensland	M.B. B.S.
South Australia	University of Adelaide	M.B. B.S.
	Flinders University of South Australia	B.M. B.S.
Tasmania	University of Tasmania	M.B. B.S.
Victoria	University of Melbourne	M.B. B.S.
	Monash University, Victoria	M.B. B.S.
Western Australia	University of Western Australia	M.B. B.S.
Hong Kong	University of Hong Kong	M.B. B.S.
	Chinese University of Hong Kong	M.B. Ch.B.
New Zealand	University of Auckland	M.B. Ch.B.
	University of Otago	M.B. Ch.B.
Singapore	National University of Singapore	M.B. B.S.
South Africa	University of Cape Town	M.B. Ch.B.
	University of Natal	M.B. Ch.B.
	University of the Orange Free State	M.B. Ch.B.
	University of Pretoria	M.B. Ch.B.
	University of Stellenbosch	M.B. Ch.B.
	University of Witwatersrand	M.B. B.Ch.
West Indies	University of the West Indies	M.B. B.S.

registration. Those holding these qualifications are also eligible for provisional registration. Applicants for registration must comply with certain other conditions. Leaflets and forms of application may be obtained from the office of the Overseas Registration Division of the Council.

APPENDIX 2

TESTS FOR LIMITED REGISTRATION

In order to practise medicine in the United Kingdom, a doctor who has qualified overseas and who is not eligible for full registration must hold limited registration.

The General Medical Council may grant limited registration to a doctor who:

(a) has been selected for employment in an approved hospital or other institution;

(b) has obtained overseas medical qualifications which the Council accepts for the purposes of limited registration;

(c) has the necessary knowledge of English;

(d) is of good character; and

(e) has the necessary professional knowledge and skill, and has acquired the relevant experience.

Limited registration—which can only be granted for a maximum period of five years—only covers employment under the supervision of a fully registered medical practitioner.

Doctors who seek limited registration are obliged to pass, or to be exempted from, a test designed to assess both professional knowledge and linguistic skills: the Professional and Linguistic Assessments Board (PLAB) Test. This test comprises:

— an MCQ paper to test factual professional knowledge in each of the main branches of medicine;

— a tape-recorded test of comprehension of spoken English;

— a clinical problem solving examination to assess the ability to apply professional knowledge in a variety of clinical situations, to interpret symptoms, signs and investigations and to give instructions for the care and management of patients;

— a written English examination to test the ability to understand written English and to write clearly and distinctly in English;

— a projected material examination (i.e. questions based on projected slides) to assess clinical knowledge and management in each of the main branches of medicine; and

— an oral examination to assess ability to converse in English and to apply professional knowledge to clinical problems.

Applicants should note that admission to the test will not be granted by the GMC unless the doctor has satisfactorily completed overseas, *after qualifying*, appropriate experience of not less than 12 months' duration which is acceptable to the Council.

Applications to take the Test should be addressed to the Registrar, General Medical Council.

EXEMPTIONS

To secure exemption from the PLAB Test, five criteria have to be met:

(a) suitability for postgraduate training which must be vouched for by a sponsor overseas with personal knowledge of the applicant;

(b) adequate postgraduate experience must have already been completed;

(c) ability in English must be both adequate and attested to by the sponsor;

(d) the training programme in the U.K. must be prearranged and satisfactory to the GMC; and

(e) the training itself must be supervised.

(f) must not have failed the PLAB test within five years of obtaining a medical degree; cases of failure after five years are assessed individually by committee.

PROCEDURE

Applicants for PLAB exemption should note that the procedure takes at least six months, both to obtain the necessary documents and to allow the GMC to process them. Trainees should not arrange to arrive in the U.K. before they have been *assured* of exemption.

Further information is obtainable from The Registrar, General Medical Council, Overseas Training Division.

Royal College of Anaesthetists Guide to Basic Specialist Training

1. INTRODUCTION

1.1 ROLE OF THE COLLEGE OF ANAESTHETISTS

The Royal College of Anaesthetists plays an important role in maintaining standards of basic specialist training (BST) by "recognizing" hospitals as suitable for training a specified number of senior house officers (SHOs) and/or registrars.

Hospitals seeking recognition must submit applications on the prescribed form. The College then appoints a Visitor to assess the hospital, make additional enquiries and discuss the educational programme with the consultants and trainees.

The application form indicates the points about which the College needs to be satisfied before granting approval. The decisive factor, however, is evidence of the willingness and ability of consultants to educate their trainees and of adequate opportunity for study for those in the training grades. Confidential interviews with junior staff, in addition to discussion with the consultant staff are a normal part of these visits. Another important role of the College is to provide consultants with the necessary support to raise their own standards.

It is important for the hospital to establish with the Visitor a mutually convenient date as soon as possible after first contact so that Visits are not unduly delayed.

1.2 THE HOSPITAL RECOGNITION COMMITTEE

The Visitor's report is received by the College's Hospital Recognition Committee (HRC). This committee has cross representation with the HRC of the Royal College of Surgeons of England and the HRC of the Royal College of Obstetricians and Gynaecologists. In straightforward cases, the HRC makes a recommendation to Council of the Royal College of Anaesthetists whose decision is communicated to the hospital concerned. In other cases, the HRC may request further information from its Regional Educational Adviser or other sources. All decisions regarding recognition are decisions of Council of the Royal College of Anaesthetists.

1.3 SCHEDULING OF POSTS

The College recognizes training posts in hospitals as Schedule I or Schedule II. The difference lies not in the quality or quantity of teaching but in the breadth of experience offered. A post is graded as Schedule II only, because it is in one of the smaller district general hospitals or it may be because it is in a highly specialized hospital dealing only with for example, paediatric surgery or cardiac surgery. The number of hospitals in this category is steadily decreasing as comprehensive rotational schemes are being introduced but the category may continue to be applied to training posts which are not included within a rotational scheme even although the other, rotating posts, in the hospital may be classified as Schedule I.

Schedule I classification indicates that trainees may spend all of the necessary two years of BST in that hospital or hospital grouping. Where Schedule II classification for a post is granted the trainee may not claim more than one year or a shorter agreed period specified by the College towards the two years of BST necessary for eligibility for the final F.R.C.Anaes. examination.

Recognition for training can be conferred for a maximum period of five years although, where problems have been identified, a lesser period may be specified. The College may consult with Regional Educational Advisers and others to ensure that the quality of training is maintained throughout the recognition period. Any alterations in the number of posts for which recognition has been granted should be notified to the College. Where consultants feel that the circumstances are changing to the advantage or detriment of their educational programmes, they should consult the College and may request a re-visit before the recognition period has elapsed.

Recognition is normally granted only for established posts in the grades of SHO and registrar. For those holding part-time posts, recognition should be sought on an individual basis.

1.4 RELATIONSHIP OF HOSPITAL RECOGNITION TO THE F.R.C.Anaes.

The regulations for the Part 3 F.R.C.Anaes. require that candidates shall have held, for not less than two years or its equivalent part-time, a post or posts in anaesthesia approved by the College for this purpose. At least one year or its equivalent part-time must be spent in a Schedule I post.

The aim is to ensure that candidates should have had adequate training in a wide range of clinical practice and should have acquired their anaesthetic education in hospitals which provide a high standard of service to the patient.

Failure to meet the College criteria for BST may lead to a loss of educational recognition by a hospital. In this event, there is no detriment to those already in post but posts in the hospital cannot be re-advertised as having training recognition until this has been restored by the College.

2. CLINICAL EXPERIENCE

2.1 ANAESTHETIC EXPERIENCE IN GENERAL

Ideally candidates should obtain some experience in all branches of anaesthesia and allied subjects but the College recognizes that this may not always be feasible.

The College does not define in detail what is required but rather offers general guidance as to what will be acceptable for full recognition. This may be gained within the post, on rotation to other hospitals or by attendance at familiarization or similar courses (see para 5.4).

The College stresses that trainees must have consultant support available throughout the 24 hours. Trainees should know to whom they should turn for advice and help with anaesthesia for elective surgery as well as with emergency work. In particular, trainees should not be expected to work unsupervised in isolated locations.

For inclusion in Schedule I, hospitals or rotational schemes should offer experience in all the fields listed under A in Appendix 1, together with most, but not necessarily all those listed under B. The experience offered in the fields listed under B should be made available to the trainee at an appropriate stage of training and not merely left until the end of a long and complex rotational programme involving significant levels of service commitment.

Where a sufficient range of experience cannot be provided, individual posts may be eligible for recognition under Schedule II.

There are certain spheres of experience which are of fundamental importance to good BST and these are listed below.

2.2 PAIN MANAGEMENT TRAINING

The prime function of an anaesthetist is to prevent or relieve pain. The acquisition of essential knowledge about the management of pain should form an integral part of an anaesthetist's training from an early stage. During BST, the trainee should acquire experience in the assessment, diagnosis and management of pain. A designated consultant should be responsible for the co-ordination of the training which must include:

Basic sciences

(a) Basic knowledge of afferent and efferent pathways, peripheral and central mechanisms of pain generation, transmission, modulation and appreciation.

(b) The pathophysiology of injury.

(c) The assessment of pain.

(d) Physiological and psychological basis of pain management.

(e) Pharmacology:

- (i) primary and secondary analgesics,
- (ii) local anaesthetic agents,
- (iii) other drugs used for control of symptoms.

Clinical sciences

(a) Application of drug therapy, including methods of delivery.

(b) The role of neural blockade and knowledge of commonly employed techniques.

(c) Stimulation-produced analgesia.

2.3 PRE- AND POSTOPERATIVE VISITS

All anaesthetists should make adequate preoperative assessment of their patients and monitor their performance by carrying out postoperative visits. Wherever possible, pre-anaesthetic visits should be made by the anaesthetist who subsequently gives the anaesthetic.

Departments or units in training hospitals should initiate and maintain policies for the relief of acute pain as described in the report of the Working Party on "Pain after surgery" in the Commission on the Provision of Surgical Services, jointly prepared by the Royal College of Surgeons of England and the Royal College of Anaesthetists, September 1990.

2.4 OBSTETRIC ANAESTHESIA AND ANALGESIA

2.4.1 Basic specialist training in anaesthesia must include obstetric anaesthesia and analgesia. The minimum provision is as follows:

(i) A consultant anaesthetist in charge of training in obstetric anaesthesia and analgesia. Arrangements must be made for the trainee to receive adequate instruction in the care of the obstetric patient.

(ii) Consultant support available throughout the 24 hours.

(iii) Instruction and practice in obstetric anaesthesia including related postoperative and intensive care.

(iv) Instruction and practice in a variety of methods of pain relief in labour including extradural analgesia. This should include the management of after-effects and recovery. Training must include designated duty for the care of obstetric patients on a continuing basis. Trainees should be as free as possible from other duties to enable them to devote themselves to full-time care. Responsibility solely for inserting extradural catheters is not sufficient.

(v) At least daily contact between the consultant on duty for the labour ward and the trainee.

(vi) Instruction and practice in neonatal resuscitation.

(vii) Adequate trained assistance for the anaesthetist at all times.

(viii) Sufficient practical experience of general and regional anaesthesia and analgesia for obstetrics under appropriate supervision by the completion of basic specialist training.

(ix) Satisfactory liaison between related professional groups.

2.4.2 Both the Royal College of Anaesthetists and the Royal College of Obstetricians and Gynaecologists have agreed that in the interests of patient safety, a person proficient in cardiopulmonary resuscitation of a pregnant woman should be available within the maternity unit at all times if an extradural is in place.

2.4.3 It is not possible for guidance to be given on the numbers and types of cases to which the trainee should be exposed but College visitors will wish to satisfy themselves that the nature and number of cases treated, and the instruction given on them provide the trainee with adequate training in the management of obstetric patients.

2.4.4 Training programmes which include hospitals which cannot offer adequate instruction in obstetric work may still be recognized within a Schedule I scheme if the trainees are seconded or rotated to a recognized obstetric unit. This will require not less than the equivalent of one month of whole-time attachment, including on-call duty, to an obstetric unit with sufficient facilities for the trainees. Familiarization courses alone cannot be regarded as providing adequate instruction in obstetric work for BST.

2.5 INTENSIVE THERAPY

2.5.1 Basic specialist training in anaesthesia must include adequate instruction in the care of patients in an Intensive Therapy Unit (ITU)*. The minimum provision is as follows.

(i) A designated and adequately equipped ITU with at least four beds which regularly deals with patients who could not be monitored or managed in a general ward or high dependency unit.

(ii) A consultant in administrative charge of the ITU.

(iii) Consultant support available for the ITU throughout the 24 hours. The consultant responsible for the ITU need not be an anaesthetist provided adequate instruction is given to trainee anaesthetists.

(iv) At least daily contact between the consultant on duty for the ITU and the trainee.

(v) Senior medical cover immediately available at all times to deal with emergency calls to the ITU.

*As defined by the Association of Anaesthetists of Great Britain & Ireland and by the Intensive Care Society.

(vi) Specifically trained and designated ITU nursing staff.

(vii) Training must include designated duty for the bedside care of patients on a continuing basis. Trainees should be as free as possible from other duties to enable them to devote themselves to full-time care. Responsibility solely for artificial ventilation is not sufficient.

2.5.2 It is not possible for guidance to be given on the numbers and types of cases to which the trainee should be exposed but College visitors will wish to satisfy themselves that the nature and number of cases treated, and the instruction given on them provide the trainee with adequate training in the management of patients in an ITU.

2.5.3 Training programmes which include hospitals which cannot offer adequate instruction in ITU work may still be recognized within a Schedule I scheme if the trainees are seconded or rotated to a recognized ITU. This will require not less than the equivalent of two months of whole-time attachment, including on-call duty, in an ITU with sufficient facilities for accepting the trainees. Familiarization courses alone cannot be regarded as providing adequate instruction in ITU work for BST.

2.6 RESUSCITATION

Trainees should become experienced at resuscitation at an early stage in training. They should receive theoretical instruction and practical experience of the management of resuscitation, preferably with the cardiac arrest team. There must be provision of adequate resuscitation equipment, a record system and an effective call mechanism.

2.7 REGIONAL ANALGESIC TECHNIQUES

Trainees should receive tuition and experience in spinal and extradural analgesia for operative surgery and postoperative pain relief and in a reasonable range of other types of nerve block. They should also understand and have experience of intravenous regional analgesia.

2.8 CHRONIC PAIN RELIEF

Although extensive practical involvement in the management of chronic pain services is more appropriate to HST, trainees at BST level should be aware of the work of a pain clinic, the techniques involved and have opportunities to attend treatment sessions.

2.9 SURGICAL SUB-SPECIALTIES

Experience in anaesthesia for certain surgical subspecialities such as cardiothoracic surgery, neurosurgery, and neonatal surgery may be limited and has frequently therefore been confined to HST. Rotational training schemes will make opportunities to participate in these sub-specialties more readily available. For the purposes of BST, however, it is sufficient for trainees to have been educated in the underlying principles and to have familiarization visits to appropriate units. In planned rotational programmes it is anticipated that opportunities would be made available for trainees to make such visits within BST.

2.10 PATIENT RECORDS

Hospitals requesting recognition are asked to provide a copy of their patient anaesthetic record form and the College visitor will wish to see how these are kept, filed and what retrieval system is employed. The same applies to ITU records.

3. GENERAL FACILITIES

3.1 ANAESTHETIC ROOMS AND OPERATING THEATRES

It is expected that all locations where anaesthetics are administered will be adequately equipped and staffed when in use.

In particular, good training demands adequate facilities for monitoring patients during anaesthesia. Appendix 2 shows the facilities which should be available in recognized hospitals. Group A items should be in all locations where anaesthetics are administered and Group B items should be in one or more locations whence they can easily be obtained when required. These lists are intended as guidelines which will be liable to revision with advancing technology.

None of this equipment, however, diminishes the need for the most important monitor of all—continuous care by an anaesthetist.

3.2 RECOVERY FACILITIES

The existence of satisfactory recovery facilities is essential. The minimum provisions of the recovery area acceptable for recognition are that:

3.2.1 Anaesthetists must be able to hand patients over to specifically trained and designated nursing staff who must be available for the care of all post-anaesthetic patients until they can safely leave the recovery area.

3.2.2 A recovery nurse must not have other duties while caring for a post-anaesthetic patient.

3.2.3 Adequate equipment for monitoring the vital functions of patients and for resuscitation must be available in the recovery area. This includes an appropriate number of pulse oximeters and automatic blood pressure recorders.

3.3 ASSISTANCE FOR THE ANAESTHETIST

No anaesthetist should be expected to work without a properly trained assistant, whether an Operating Department Assistant or a trained anaesthetic nurse. This applies to all locations where anaesthetics are given, day and night.

3.4 DEPARTMENTAL PREMISES, SECRETARIAL HELP AND ORGANIZATION

There should be a focal point for the anaesthetic staff so that an effective service can be co-ordinated and optimal opportunities provided for gaining experience and teaching. This can only be achieved by having proper premises and adequate secretarial support.

Premises should include, as a basic minimum, adequate consultant office accommodation, secretarial accommodation, and a trainee common room. The anaesthetic department should be located centrally, as close as possible to a main theatre suite and/or intensive care unit. Other facilities such as a seminar room, a library and a quiet area for study must be provided. For larger departments these form an essential integral part of required accommodation.

4. STAFFING

4.1 CONSULTANT STAFF

A BST programme needs to have an adequate number of involved consultants. A two-year training programme is unlikely to be effective in a department with less than four whole-time or maximum part-time consultants. Such small departments may of course provide excellent training as part of a larger rotational scheme.

4.2 TRAINEES

The number of trainees is also important in relation to training, both as a ratio to the number of consultants and as an absolute number. Duty rotas not more arduous than a one in three arrangement are expected. Therefore, unless there are other grades to provide a first-on-call service it is probable that there will be a minimum of four trainees working a nominal one in four rota.

Trainees must have adequate opportunity for study. Time should be allocated free from clinical commitments, for day release or private study. Staffing levels must be adequate for this purpose.

4.3 CONSULTANT/TRAINEE RATIO

In general, the number of trainees should approximate to the number of consultants (whole-time equivalents). In obstetric anaesthesia, intensive therapy, pain management and resuscitation services, named consultants must be responsible for organizing supervision and training.

4.4 OTHER STAFF

Associate specialists, hospital practitioners, clinical assistants and staff grades are not in training posts but they may play a role in the provision of the anaesthetic service thus releasing trainees for educational purposes. Supervision and teaching of the trainee must remain primarily the responsibility of the consultant staff.

5. EDUCATION

5.1 EDUCATIONAL RESPONSIBILITIES OF CONSULTANTS

All consultants working in a recognized hospital have a duty to teach their trainee anaesthetists. They are also expected to participate in departmental meetings as part of their own continuing education as well as to set an example to trainees. In addition, consultants are expected to update their own knowledge by attendance at local and national meetings and courses, reading journals and taking study leave in accordance with their Terms and Conditions of Service.

5.2 AUDIT

It is essential for there to be adequate means of auditing the activities of the anaesthetic department. This will include careful record keeping and means of retrieval of information, regular mortality and morbidity meetings to review current practice, and maintenance of registers of critical incidents and cardiac arrests.

5.3 TRAINEE DUTIES

All trainees should have regular teaching contact with consultants in the operating theatre. The number of lists undertaken with a consultant will depend upon the experience of the trainee but should not fall below an average of three half day lists each week. It is essential that during these teaching sessions the consultant and the trainee work together throughout the list. It is not sufficient for the trainee merely to act as a helper in an adjacent theatre.

5.4 EDUCATIONAL PROGRAMME

In-service teaching in theatres should be supplemented by tuition at meetings, tutorials, journal clubs and ward rounds. Provision must be made for instruction in the basic sciences relevant to anaesthesia, either within departmental teaching or by attendance at suitable courses elsewhere. Systematic teaching courses for examinations may be arranged but this does not reduce the need for a departmental educational programme.

Trainees have a study leave entitlement and departments should ensure that it is used to good effect. In addition to attendance at courses and other educational activities, study leave may also be taken for private study.

5.5 ROTATIONS, SECONDMENTS AND FAMILIARIZATION PROGRAMMES: ORGANIZATION OF ROTATIONS

Rotations enable trainees to work in a variety of hospitals which allow them to obtain a wider range of experience, and both clinical and academic training in anaesthesia and intensive care, than could be provided in many single district hospitals. Rotations should be organized in such a way that the trainee has planned periods of training in different hospitals or units. Such periods should be of sufficient duration:

(a) to allow a trainee to feel stable and part of the department in which he or she is working;

(b) to allow a trainee to acquire the specialized training available in certain hospitals or units.

As a general rule, components of such rotations should not be of so brief a duration that the trainee is constantly on the move, especially at times when the trainee may be preparing for examinations.

Secondments and familiarization programmes

Where it is necessary to arrange secondments to other hospitals or units to allow specialized training, these should:

(a) be organized in such a way that the visiting trainee does not have to compete with other local trainees for "hands-on" experience;

(b) be organized sufficiently far ahead that they do not coincide with periods in which the trainee is preparing for an imminent examination.

5.6 LIBRARY

Libraries should provide a range of current textbooks suitable for the various parts of the F.R.C.Anaes. examination and a number of anaesthetic journals. The minimum should include the British anaesthetic journals and at least one from overseas. In addition, at least one comprehensive bench book should always be available close to locations where anaesthetics are administered.

5.7 TRAINEE RECORDS—LOG BOOKS

One consultant, who may be the College Tutor, should be in overall charge of education within the hospital or group and should be responsible for maintaining records of trainees' progress.

All trainees are strongly encouraged to maintain a record of the clinical work which they have undertaken. This is best done by the use of a log book and College Visitors will ask to inspect the log books of trainees as a means of assessing the breadth of training received. The College produces a log book which is suitable for the purpose.

5.8 CAREER ADVICE

Any consultant may be asked by a trainee for advice on training and career prospects. The College Tutor, however, has a particular responsibility in this field.

It may be helpful in large departments and for trainees in rotational training schemes for the trainee to have a personal Mentor to whom it is possible to turn to discuss progress or problems. Such a system helps to prevent isolation in the early stages of training, allows a good evaluation of the trainee's progress to be made and can often prove most helpful to the department organizer in the allocation of duties.

6. The purpose of these criteria is to ensure that a candidate for the Part 3 F.R.C.Anaes. examination shall have:

(a) received education in a department or in a rotational scheme providing a good anaesthetic service for patients;

(b) had sufficient opportunity of working with and watching consultant anaesthetists;

(c) had reasonable opportunities for study;

(d) had an adequate range of anaesthetic experience;

(e) developed the discipline of self-audit.

APPENDIX 1

For inclusion in Schedule I, individual hospitals or groups of hospitals in approved rotational schemes should offer trainees experience in all the fields under A, together with most, but not necessarily all, of those listed under B. Where a sufficient range of experience cannot be offered in a hospital or to a particular trainee who is not part of an approved rotational scheme the hospital experience gained may only be recognized under Schedule II.

A. Basic experience

General surgery
Orthopaedic surgery
Obstetrics and gynaecology
Emergency surgery including trauma
Surgery for children (excluding neonates)
Otorhinolaryngology
Day care surgery
Intensive therapy
Resuscitation
Managment of pain

B. Specialized experience

Dental surgery (ambulant)
Diagnostic procedures
Radiotherapy
Oncology
Ophthalmology
Thoracic Surgery (see para 2.9)
Cardiac Surgery (see para 2.9)
Neurosurgery (see para 2.9)
Neonatal surgery (see para 2.9)
Plastic and maxillo–facial surgery

APPENDIX 2

The following facilities should be available in recognized hospitals. Group A items should be in all locations where anaesthetics are administered and Group B items should be in one or more locations from whence they can easily be obtained when required.

Group A

Oxygenation	Oxygen failure warning device Oxygen analyser Pulse oximeter
Ventilation	Ventilator disconnection alarm Respirometer (e.g. Wright's) End-tidal carbon dioxide analyser
Circulation	Pre-cordial or oesophageal stethoscope ECG monitor Automatic blood pressure recorder
Temperature	Thermometer
Neuromuscular transmission	Peripheral nerve stimulator Syringe drivers or pumps

On display should be algorithms for the management of: cardiac arrest, hypersensitivity reaction and malignant hyperpyrexia.

Group B

Direct arterial pressure monitoring.
Means of measuring CVP.
Means of measuring pulmonary artery pressure.

Joint Committee for Higher Training of Anaesthetists—Guide to Higher Specialist Training

INTRODUCTION

The Joint Committee for Higher Training of Anaesthetists consists of representatives of the Royal College of Anaesthetists, the Scottish Standing Committee of that College, the Faculty of Anaesthetists of the Royal College of Surgeons in Ireland, the Association of Anaesthetists of Great Britain and Ireland, and the Association of University Professors of Anaesthesia. Its constitution and terms of reference are stated in Appendix 1.

The Scheme of Higher Training described in this Memorandum is intended to help the prospective consultant anaesthetist to obtain the best possible training and to have access to the best available advice in pursuing it.

Training programmes must provide the widest possible range of anaesthetic experience but the Joint Committee recognizes the importance of flexibility and of adapting training programmes to the individual abilities and preferences of trainees. This Memorandum should therefore be read as a general outline of recommendations for the guidance both of trainees and of teachers, and not as an indication of the Joint Committee's intention to direct training in a restrictive way.

CONTENT OF HIGHER TRAINING

1. CLINICAL EXPERIENCE

Higher Specialist Training in anaesthesia should be a logical continuation of the Basic Training which leads to the acquisition of the diploma of F.R.C.Anaes. or F.F.A.R.C.S. Ire. In addition to providing experience and training in those aspects of anaesthesia to which the trainee did not have adequate exposure during pre-Fellowship training, the Higher Training period should give to the prospective consultant progressively increasing responsibility and the opportunity to undertake, under consultant supervision, all the duties that he or she will eventually discharge independently.

The objective is to ensure that trainees are given the opportunity to gain experience, both in breadth and in depth, in a wide range of cardiothoracic, neurosurgical and paediatric work and the opportunity to become fully familiar with those other activities, such as intensive care and pain therapy, with which anaesthetists are involved, taking due account of experience in highly-specialized work that trainees may have obtained before entry into Higher Specialist Training. It must be understood that it is impossible for every Higher Training Programme to provide experience in every aspect of the specialty. Experience in highly specialized work, for example, cardiac, paediatric, neurosurgical, should not normally be repeated in a training programme unless it is specifically designed to equip an individual for a career in such a specialized field of anaesthesia.

Accreditation will depend on satisfactory completion of an appropriate period of Higher Specialist Training acquired in Joint Committee for Higher Training of Anaesthetists-approved programmes. Allowances can be, and are, made for local variation in training programmes throughout the United Kingdom and Republic of Ireland, but they must make provision for the acquisition of complementary teaching and district hospital experience. As a general rule, it is expected that trainees should, before accreditation, have spent at least 12 months in a designated teaching hospital, and not more than 18 months in a district general hospital. Training schemes should not normally cross regional boundaries.

2. TEACHING EXPERIENCE

Trainees should attend regular clinical meetings with staff and should undertake some responsibilities for the training and teaching of junior anaesthetists, auxiliary staff and medical undergraduates. In particular, they will be expected to take part in the giving of in-service lectures and tutorials to junior anaesthetists undergoing Basic Specialist Training.

3. RESEARCH

The period of Higher Training offers opportunities for research activities and the Joint Committee believes that every encouragement should be given to the trainee to take advantage of these, under appropriate guidance. In most cases it will be sufficient for the trainee to participate in some clinical investigation and thus to experience the difficulties and pitfalls involved in research and to learn how to assess the published work of others. Publication of work should be encouraged.

A period of up to one year whole-time in a relevant University department or other approved institution in the United Kingdom, Republic of Ireland or overseas may be accepted by the Joint Committee towards accreditation, provided that the experience has been acquired in a post either specifically recognized by the Joint Committee or in respect of which prospective approval (of the proposed research) has been obtained from the Joint Committee. *As the latter case is more common, the importance of obtaining prior approval from the Joint Committee is stressed.*

4. ACADEMIC POSTS

The continued advance of the specialty is dependent upon the maintenance of academic capability in teaching and in clinical and fundamental research. The Joint Committee regards it as of high priority to offer encouragement to young anaesthetists to commit themselves to an academic career and recognizes that special arrangements have to be made with the academic departments if this is to be realized.

As academic research training demands great application and hard work in addition to that required to reach consultant status, the Joint Committee recognizes that some relief from routine tasks must be arranged for those holding university lecturer and research appointments, to enable them to complete Higher Training within a time which is not so unreasonably long as to act as a deterrent.

In general the totality of clinical experience will be expected to be equivalent to that recommended for senior registrar training schemes. The Joint Committee expects this to be arranged so that it will take no longer than three years in most academic posts but there will be individual variations which will be related to the academic and research standard which will be concurrently achieved.

The Joint Committee appreciates that local circumstances are so variable that no all-embracing regulation will be successful in fostering this wish to provide for the future and *it is prepared to discuss proposed programmes of training for individual trainees with the academic departments.*

5. EXPERIENCE OF ADMINISTRATION

Programmes approved for Higher Training should include a period during which the trainee can participate in (acquire experience of) departmental/divisional administration and budgeting. This will enable the prospective consultant to acquire the knowledge and assume the responsibilities connected with the efficient operation of clinical services in the Health Service.

6. SERVICE OUTSIDE THE UNITED KINGDOM OR REPUBLIC OF IRELAND

A maximum of one year of training experience acquired under supervision in a centre outside the United Kingdom or Republic of Ireland may be accepted towards accreditation. *Approval of such experience must be obtained prospectively,* as no centre outside the United Kingdom or Republic of Ireland is specifically approved for Higher Training by the Joint Committee. Whilst trainees are at liberty to spend a period in excess of one year overseas, a certificate of accreditation will not be granted before completion of two years of approved Higher Training in an established post in the United Kingdom or Republic of Ireland. The Joint Committee understands the need for flexibility with regard to overseas experience, but approval can only be given if the experience can be shown to have relevance to Higher Training in the specialty of anaesthesia.

It should be stressed that trainees offering overseas experience towards accreditation will be required to obtain satisfactory reports of such experience from the overseas supervisors of their training.

DURATION OF HIGHER TRAINING

Higher Training will normally occupy a minimum of three years of which at least two must be spent in clinical anaesthesia as a senior registrar in a specifically approved post. *Up to one year of experience gained after passing a Final Fellowship examination may be accepted towards accreditation, comprising either (a) locum or temporary senior registrar posts (which may be included in the two years of clinical anaesthesia defined above) and/or (b) post-Fellowship registrar or overseas experience (which may be included in the third year).* Normally, such experience can only be taken into consideration when trainees obtain *an established (i.e. not a temporary or locum)* senior registrar post. Claims for the acceptability of such experience must be supported by the appropriate consultants in charge of training, who will be required to satisfy the Joint Committee that the duties and responsibilities of the post have been consistent with senior registrar status. The Joint Committee will only accept experience acquired in locum consultant posts where such experience has been obtained during the final three months of the final year of higher training.

A certificate of accreditation will not be granted to a trainee who has not acquired a minimum of five years experience in the specialty of anaesthesia. The Joint Committee will not count towards accreditation post-Fellowship experience acquired in non-training posts such as staff grade, associate specialist or clinical assistant.

PART-TIME TRAINING

The Joint Committee will consider the submission of part-time training programmes for senior registrars, on condition that the programmes provide for a minimum contribution from part-time trainees of five clinical sessions per week plus adequate provision for emergency work. Part-time training can only be counted towards accreditation where it has been undertaken in hospitals approved by the Committee and where the programme has been given prior approval.

The accreditation of part-time trainees will be recommended when they have acquired, in aggregate, the equivalent of three years of whole-time senior registrar training.

ORGANIZATION OF TRAINING PROGRAMMES

It will be seen that the period of Higher Training coincides approximately with the present senior registrar period. However, some existing senior registrar posts will not alone provide a sufficiently wide range of experience. Approval of such posts will depend on the provision of external attachment or secondment to special units, or incorporation in rotational schemes with other hospitals.

When inspecting programmes for which approval is sought, the Joint Committee will consult and co-operate with the appropriate Regional Postgraduate Educational Committees, Regional Educational Advisers and with those consultants who are responsible for the supervision of the trainees. A list of approved programmes will be published from time to time.

It should be stressed that, although the Joint Committee will be pleased to offer advice on the organization of training programmes, the responsibility for the planning and supervision of programmes and of adapting them to the needs of individual trainees rests with the consultants in charge of training at local level. Every training programme should have a designated Co-ordinator of Senior Registrar Training, who should organize regular, preferably annual, reviews of each senior registrar's progress.

It should also be borne in mind that the Joint Committee's approval of Higher Training is usually given to programmes of training, as distinct from recognition of a succession of individual posts, although the need to preserve a number of specialized posts unconnected with rotational programmes is recognized.

ENROLMENT AND ACCREDITATION

On entry into an approved Higher Training Programme, the trainee should apply for enrolment with the Joint Committee. No fee will be charged for enrolment. Eligibility for enrolment will depend on the possession of the F.R.C.Anaes. or F.F.A.R.C.S. Ire. diploma, or of acceptance by the Joint Committee of evidence of completion of comparable anaesthetic training. On completion of the designated period of Higher Training, the Joint Committee will ask for a report from the appropriate consultant in charge of training to the effect that the period of higher training has been carried out satisfactorily, providing details of the trainee's exposure to highly-specialized experience, and stating that the trainee is to be regarded as having satisfied the minimum requirements of the Royal College of Anaesthetists and the Faculty of

Anaesthetists, Royal College of Surgeons in Ireland for the assumption of consultant status.

Upon receipt of the report the Joint Committee will recommend to the appropriate College or Faculty (that of which he or she holds the Fellowship) the granting of a Certificate of Accreditation, again without fee.

Accreditation will represent a clear recognition by the College or Faculty of the holder's eligibility for consultant responsibility, although it cannot in itself be a guarantee of appointment to that grade, or of suitability for a particular consultant post, which will be determined by the Health Authority on the recommendation of a statutory Advisory Appointments Committee.

OVERSEAS GRADUATES

It is envisaged that a sufficient number of approved Higher Training programmes will be available to accommodate both those who have completed Basic Specialist Training in the British Isles and those who come from overseas with equivalent experience and qualifications and who wish to obtain Higher Training in anaesthesia. Individual applications for recognition of equivalence of Basic Specialist Training may be considered on their merits but the following qualifications will be accepted by the Joint Committee as equivalent, for this purpose, to the F.R.C.Anaes. or F.F.A.R.C.S. Ire.:

Fellowship in the Faculty of Anaesthetists of the Royal Australasian College of Surgeons.

Fellowship in the Faculty of Anaesthetists of the College of Medicine of South Africa.

Diploma of the American Board of Anesthesiology.

Fellowship of the Royal College of Physicians and Surgeons (Canada) in Anaesthesia.

Overseas graduates who seek a certificate of accreditation will normally be required to obtain a minimum of two years of senior registrar experience in approved programmes or posts in the United Kingdom or Republic of Ireland.

ARMED FORCES

Special requirements apply to trainees in the Armed Forces. In summary, these trainees will be eligible for accreditation in the usual way, provided that their post-Fellowship training has been obtained in Services hospitals approved by the Joint Committee and that not less than 18 months of Higher Training has been acquired by means of secondment to approved civilian hospitals in the British Isles, for the provision of specialized experience not available in Services hospitals. Further particulars can be provided by the Joint Services Educational Adviser to the College of Anaesthetists.

CONCLUSION

The Joint Committee wishes to stress that the Scheme described in the foregoing paragraphs is designed to provide a broadly-based programme of post-Fellowship training, leading to accreditation. Its recommendations are intended to be capable of flexibility in interpretation and to allow for local variations.

It should also be emphasized that accreditation represents the attainment of minimum requirements for consultant appointment, and that possession of a Certificate of Accreditation does not imply that all holders are equal, since they will demonstrate widely differing abilities and ambitions, and varying specialized experience.

If a doctor who has not followed a pattern of post-Fellowship training as recommended by the Joint Committee applies for a consultant post, anaesthetist assessors, appointed by the College or Faculty on Advisory Appointments Committees are free to evaluate the curriculum vitae of the applicant, in accordance with the College and Faculty Criteria for Consultant Status, and to recommend, if appropriate, that the applicant is suitable for appointment.

Further information or advice can be obtained from: The Secretary, Joint Committee for Higher Training of Anaesthetists, 48/49 Russell Square, London WC1B 4JP.

APPENDIX I

CONSTITUTION AND TERMS OF REFERENCE OF THE JOINT COMMITTEE

CONSTITUTION

The Joint Committee for Higher Training of Anaesthetists is constituted as follows:

Five representatives of the Council of the Royal College of Anaesthetists.

One representative of the Standing Committee, Scotland, of the Royal College of Anaesthetists.

Three representatives of the Board of Faculty of Anaesthetists of the Royal College of Surgeons in Ireland.

Two representatives of the Association of Anaesthetists of Great Britain and Ireland.

Two representatives of the Association of University Professors of Anaesthesia.

One representative of Regional Postgraduate Deans.

One junior staff representative.

The Committee shall have the power to co-opt.

TERMS OF REFERENCE

(i) To keep under general review the working of the scheme of Higher Anaesthetic Training.

(ii) To consider and advise on matters of policy relating to the scheme.

(iii) To keep appropriate bodies informed of the progress of the scheme.

(iv) To draw up, after inspection, a list of approved posts, and to keep these under review.

(v) To keep a roll of trainees.

(vi) To recommend to the appropriate College or Faculty that a Certificate of Accreditation be issued to those candidates who have completed an approved programme of training.

(vii) To give advice to consultants or trainees on individual variations from approved programmes.

APPENDIX II

CRITERIA FOR THE RECOGNITION OF POSTS FOR HIGHER TRAINING

When considering applications for recognition the Joint Committee will be guided by the following criteria:

(i) Higher Training programmes, whether they consist of individual posts or a series of posts, should provide clinical experience sufficient in range and depth to fulfil the requirements set out in the memorandum. Arrangements should be such as to ensure that at the completion of training a wide spectrum of experience will have been obtained.

(ii) The number and commitment of consultant anaesthetists on the staff of a hospital should be sufficient to ensure adequate supervision and education. The senior registrars' programme of work should be organized in such a way as to encourage assumption of responsibility in proportion to the trainees' experience and ability. *Therefore too much time should not be spent on work of limited educational value.*

(iii) Periods of time available for study or research should amount, in aggregate, to the equivalent of at least one day of each working week. Such professional leave, if desired and if local circumstances permit, should be allowed to accumulate over a period of more than a year to facilitate exchange or secondment to special units.

(iv) Organized postgraduate training, preferably linked with a regional scheme, must be available. Trainees should be encouraged and assisted to attend appropriate education meetings and courses. Regular departmental meetings or conferences of an education nature should be *organized and attended* by the consultant staff and the trainees should participate in the teaching of junior staff undergoing Basic Specialist Training.

(v) Higher anaesthetic trainees should have access to a library containing a good range of journals, and to indexing and abstracting services.

(vi) Departments should encourage an adequate system of anaesthetic record-keeping. Regular conferences to discuss anaesthetic mortality and morbidity should be held.

(vii) When rotation of posts is required, married accommodation, suitable for a senior registrar and his/her family, should ideally be provided within reasonable distance of each location.

APPENDIX III

A list of approved programmes and posts is available upon application.

March 1990

Calendar of Major Anaesthetic Events

The following figure represents a wall calendar illustrating the dates of major anaesthetic meetings occurring in the forthcoming year (April 1993 to March 1994), largely in the U.K. This is an attempt to provide departments with information in order to avoid clashes of meetings which tend to occur with increasing frequency. Secretaries of societies who wish to have the dates of future meetings published in this format are asked to forward the appropriate information to the editor. Final copy date for events occurring in the year April 1994–March 1995 is October 1993. The editor can accept no responsibility for inaccurate information published.

Key to diagram

AAA—Age Anaesthesia Association
ACA—Association of Cardiothoracic Anaesthetists
APA—Association of Paediatric Anaesthetists
ARS—Anaesthetic Research Society
A/AIT—Association of Anaesthetists, Anaesthetists in Training, Annual Scientific Meeting
A/ASM—Association of Anaesthetists, Annual Scientific Meeting
A/WSM—Association of Anaesthetists, Winter Scientific Meeting
C/AF—Royal College of Anaesthetists, Anniversary Forum
C/AS—Royal College of Anaesthetists, Annual Symposium
C/ASM—Royal College of Anaesthetists, Annual Scientific Meeting
C/CCT—Royal College of Anaesthetists, Course on Current Topics
C/F2—Royal College of Anaesthetists, Part 2 F.R.C.Anaes. Course
C/F3—Royal College of Anaesthetists, Part 3 F.R.C.Anaes. Course
C/PSD—Royal College of Anaesthetists, Postgraduate Study Day
EAA—European Academy of Anaesthesiology
ESRA—European Society of Regional Anaesthesia
HAS—History of Anaesthesia Society
IASP—International Association for the Study of Pain, World Congress
ICS—Intensive Care Society
NTC—Neuroanaesthetists' Travelling Club
OAA—Obstetric Anaesthetists Association
PS—Pain Society
RSM—Royal Society of Medicine, Section of Anaesthetics

The following are the *provisional* dates of the F.R.C.Anaes. examination viva weeks (week commencing):
Part 1: 28 July, 29 November, 21 March (1994)
Part 2: 21 June, 1 November, 31 January (1994)
Part 3: 12 July, 28 February (1994).

	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	SAT	SUN
APR 1993		1 ← AAA	2 PS ARS OAA RSM	3 → ARS NTC	4	5 WEEK 14	6	7	8	**9**	10	11	**12** WEEK 15	13 ←	14 C/F3	15	16 →	17	18
MAY				1 ICS	2	**3** WEEK 18	4	5	6	7 C/ASM	8	9	10 WEEK 19	11	12	13	14 RSM	15	16
JUN							1	2	3	4 RSM	5	6	7 ← WEEK 23	8	9 C/CCT	10	11 →	12	13
JUL		1	2	3	4	5 WEEK 27	6	7	8	9 ARS	10 ARS	11	12 WEEK 28	13	14	15	16	17	18
AUG					1	2 WEEK 31	3	4	5	6	7	8	9 WEEK 32	10	11	12	13	14	15
SEP							- - -	1 APA	2 ←	3 →	4 EAA	5 →	6 ← WEEK 36	7	8 C/F2	9 ←	10 →	11 ESRA	12 →
OCT			1 OAA RSM	2	3	4 ← WEEK 40	5	6 C/F3	7	8 →	9	10	11 ← WEEK 41	12	13 C/F3	14	15 →	16	17
NOV						1 WEEK 44	2	3	4 C/AS	5 C/AS RSM	6	7	8 WEEK 45	9	10	11	12	13	14
DEC								1	2	3 RSM	4	5	6 WEEK 49	7	8	9	10	11	12
JAN 1994				1	2	**3** WEEK 1	4	5	6	7	8	9	10 WEEK 2	11	12	13	14 A/WSM	15 A/WSM	16
FEB							1	2	3	4 RSM	5	6	7 WEEK 6	8	9	10	11	12	13
MAR							1	2	3	4 RSM	5	6	7 WEEK 10	8	9	10	11	12	13
	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	SAT	SUN

MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	
19 ← WEEK 16	20	21 C/F3 ←	22 A/AIT	23 → →	24	25	26 ← WEEK 17	27	28 C/F3	29	30 → ICS								APR
17 WEEK 20	18	19	20	21	22	23	24 WEEK 21	25	26	27	28	29	30	**31** WEEK 22					MAY
14 WEEK 24	15	16	17	18 ACA	19	20	21 WEEK 25	22	23	24	25 HAS	26 HAS	27	28 WEEK 26	29	30			JUN
19 WEEK 29	20	21	22	23	24	25	26 WEEK 30	27	28	29	30	31							JUL
16 WEEK 33	17	18	19	20	21	22 ←	23 WEEK 34	24 IASP	25	26	27 →	28	29	**30** WEEK 35	31 ←	APA	- - -		AUG
13 ← WEEK 37	14	15 C/F2	16	17 →	18	19	20 WEEK 38	21	22 ←	23 A/ASM	24 →	25	26	27 WEEK 39	28	29	30		SEP
18 ← WEEK 42	19	20 C/F3	21	22 → ICS	23 C/PSD	24	25 WEEK 43	26	27	28	29	30	31						OCT
15 WEEK 46	16	17	18	19 ARS	20 ARS	21	22 WEEK 47	23	24	25	26	27	28	29 WEEK 48	30				NOV
13 WEEK 50	14	15	16	17	18	19	20 WEEK 51	21	22	23	24	25	26	**27** WEEK 52	**28**	29	30	31	DEC
17 WEEK 3	18	19	20	21	22	23	24 WEEK 4	25	26	27	28	29	30	31 WEEK 5					JAN
14 ← WEEK 7	15	16 C/F2	17	18 →	19	20	21 ← WEEK 8	22	23 C/F2	24	25 →	26	27	28 WEEK 9					FEB
14 WEEK 11	15	16 C/AF	17	18	19	20	21 WEEK 12	22	23	24	25	26	27	28 WEEK 13	29	30	31		MAR
MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	

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Hammersmith Hospital,
Du Cane Road,
London,
W12 0HS.
Tel. 081-743 2030
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W1N 6DE.
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W1N 2EA.
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W1P 6DE.
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General Medical Council,
Administration Building,
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London,
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Fax 071-436 1338

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St James' University Hospital,
Leeds,
LS9 7TF.
Tel. 0532-433144
Fax 0532-426496

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Park Ridge, Illinois 60068-2573, U.S.A.

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International Anesthesia Research Society,
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Cleveland, Ohio 44131, U.S.A.
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Royal Victoria Hospital,
Grosvenor Road,
Belfast,
BT12 6BA.
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Fax 0232-240899

West Midlands Toxicology Unit,
Dudley Road Hospital,
Dudley Road,
Birmingham,
BS18 7QH.
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Fax 021-551 5562

Poison Information Centre,
Beaumont Hospital, PO Box 1297,
Beaumont Road,
Dublin 9,
Republic of Ireland.
Tel. 0001-379966
Fax 0001-376982

Edinburgh Poison Centre,
Edinburgh Royal Infirmary,
Laurison Place,
Edinburgh,
EH3 9YW.
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LS1 3EX.
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National Poison Information Service,
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Avon Ley Road,
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SE14 5ER.
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W1M 0BD.
Tel. 071-323 1531
Fax 071-637 3644

British Heart Foundation,
102 Gloucester Place,
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SW3 5UE.
Tel. 071-376 5735
Fax 071-823 3354

Cancer Research Campaign,
2 Carlton House Terrace,
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SW1Y 5AR.
Tel. 071-930 8972
Fax 071-321 8838

Chest, Heart and Stroke Association,
Tavistock House,
North Tavistock Square,
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WC1H 9JE.
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Ciba Foundation,
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Fax 071-436 2840

Imperial Cancer Research Fund,
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Fax 071-242 1510

Leverhulme Trust,
15–19 New Fetter Lane,
London,
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Mason Medical Research Foundation,
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Nile House, P.O. Box 1034,
Nile Street,
Brighton,
East Sussex,
BN1 1JB.
Tel. 0273-24411
Fax 0273-779172

Medical Research Council,
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Fax 071-436 6179

National Asthma Campaign,
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National Kidney Research Fund,
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Society of Apothecaries of London,
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London EC4 6EJ.
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Companies Supplying Anaesthetic Drugs, Equipment or Related Products

3M HEALTHCARE

1 Morley Street, Loughborough,
Leicestershire LE11 1EP
Tel. 0509-611611; Fax 0509-237288
General Sales and Marketing Manager:
M. C. Jamieson

3M Healthcare is a supplier of: Acupan tablets and injection, Tambocor tablets and injection, ECG diagnostic and monitoring electrode accessories, Tenzcare pain control system, AVI volumetric infusion pumps, Surgical drapes, masks and protective eye wear, Littman stethoscopes.

Acupan is an analgesic, available in tablet form, containing 30 mg nefopam hydrochloride per tablet, or 20 mg ml^{-1} nefopam hydrochloride in injection form. Acupan is indicated for the relief of acute and chronic pain including postoperative pain, acute traumatic, musculoskeletal, dental and cancer pain. The recommended adult dose is two tablets three times daily, increasing to three tablets if necessary. In the injection form, 20 mg is the normal dose given either i.v. or i.m. every 6 h. Elderly patients may require reduced dosage due to slower metabolism. It is strongly recommended that the starting dose does not exceed one table three times daily.

AAH MEDICAL

Unit 20, Broombank Business Park,
Broombank Road, Sheepbridge,
Chesterfield, Derbyshire S41 9QJ
Tel. 0246-451501; Fax 0246-450630
Sales and Marketing Director: Barry Marshall

AAH Medical is the exclusive U.K. distributor for Intertech Resources Inc and Marquest Medical, supplying a range of disposable anaesthesia products including bacterial breathing filters, heat and moisture exchangers, ventilator circuits, anaesthesia circuits, gas monitoring lines, anaesthesia rebreathing masks, catheter mounts and accessories. The latest addition to the range is the new vapour phase heated humidification system.

ABBOTT LABORATORIES LTD

Hospital Products Division,
Abbott House, Norden Road,
Maidenhead,
Berkshire SL6 4XE
Tel: 0628-773355; Fax 0628-773803
Anaesthetics Division: Julian Dixon
Critical Care Division: Mark Morrison

Abbott Laboratories Ltd has been established in the U.K. for over 50 years. The company employs approximately 750 people in the manufacture, distribution and marketing of a diverse range of high quality health care products. The Hospital Products Division was created in 1978 to meet the special needs of clinicians involved in anaesthesia and intensive care. Anaesthetic agents include enflurane and isoflurane which are manufactured at the Queenborough base. Abbott regional anaesthesia trays provide quality components necessary for spinal and extradural anaesthesia. The LifeCare patient-controlled analgesia PCA 4200 Infuser provides safe and effective patient-controlled delivery of analgesics via the i.v. route. Abbott have more recently introduced the Provider 5500. The Provider provides a simple cost effective approach to PCA.

In the critical care field Abbott Laboratories manufactures a complete range of monitoring products. The OX-3 system provides accurate continuous monitoring of mixed venous oxygen saturation using fibreoptic catheters and is based on three wavelength technology. The Critical Care division also supplies a range of thermodilution catheters, disposable and reusable transducers (Transpac), central venous catheters and a range of monitoring accessories, including ODM, a non-invasive method for monitoring cardiac output. The Life-Care volumetric infusion pump is equally suitable for both critical care and more general i.v. procedures. A range of five giving sets is available, each based upon a unique cassette that is incapable of pumping air. Abbott Laboratories manufactures a wide range of products for venepuncture including the Butterfly winged needle infusion set, the Abbocath-T indwelling cannula and Drum Cartridge central venous catheter. The Receptal product range is a unique closed disposable suction waste collection system also manufactured by Abbott.

ACORN COMPUTERS LTD

Fulbourn Road, Cherry Hinton,
Cambridge CB1 4JN
Tel. 0223-245200; Fax 0223-210865
Market Sector Manager: Patrick Neal

A wide range of medical software is available for Acorn computers including an Anaesthesia Research System developed at Withington Hospital, Manchester. The research system is designed to monitor depth of anaesthesia and thus reduce incidents of awareness during anaesthesia. Other medical applications available include EEG analysis, CT image enhancement, fluorescein angiography and glaucoma diagnosis.

ACTAMED LTD

10 Rishworth Street,
Wakefield WF1 3BY
Tel. 0924-200550; Fax 0924-200518
Managing Director: Adrian Turner

Actamed supplies patient monitoring devices for use in anaesthetics and intensive care, as well as the Bair-Hugger patient warming therapy. This simple, safe and effective system can be used intraoperatively or in recovery and is the single most effective method of warming according to the ASA guidelines on thermal regulation.

The tonomitor is a balloon catheter available in a nasogastric or sigmoid version. It provides intramucosal pH which is the first indicator of regional perfusion and ischaemia in the gut. The ability to predict patient outcome and determine therapy make it a valuable device for the critically ill and patients undergoing major surgery.

The extravascular Doppler is a new and simple way of having continuous cardiac output and pressure waves in the cardiac surgical patient. The Biocore pulmonary monitor calculates the correct time for ventilated patients to be weaned safely. IVOX intravascular oxygenator is still being assessed in providing support for the lungs in patients with ARF and ARDS.

ADVANCED MEDICAL DEVICES

Mantra House, Keighley,
West Yorkshire BD21 1SX
Tel. 0535-610078; Fax 0535-608028
Director: David Halsall

Advanced Medical Devices supplies PS6050, a microprocessor controlled syringe pump, designed for anaesthetic use. It has a flow range of 1–200 ml h^{-1} and a rapid infusion mode of 600 ml h^{-1}. It is simple to operate and has a large 16 character display which shows delivery rate and volume infused simultaneously. It is powered by 5 C cells and is portable with a typical battery life of 100 h. An optional mains adaptor is available. It has a comprehensive set of alarms and an accuracy of ±2%.

AH ROBINS

Huntercombe Lane South, Taplow,
Maidenhead, Berkshire SL6 0PH
Tel. 0628-604377; Fax 0628-666368
Senior Hospital Product Manager:
P. R. Evans

AH Robins' main area of interest is pharmaceuticals. Dopram (doxapram hydrochloride) is a selective ventilatory stimulant which acts primarily on peripheral chemoreceptors and can be used in acute respiratory failure. Dopram can be used also following anaesthesia to increase the rate of recovery from inhalation anaesthesia, to reduce respiratory depression associated with analgesic therapy and to reduce the incidence of postoperative complications.

Robinul injection (glycopyrrolate) is a quaternary ammonium anticholinergic agent with marked and prolonged control of salivary and pharyngeal secretions. Robinul injection is used to protect against the peripheral muscarinic actions of anticholinesterases during reversal of neuromuscular block produced by non-depolarizing muscle relaxants, before operation to reduce salivary, tracheobronchial and pharyngeal secretions and to attenuate or prevent intraoperative bradycardia associated with suxamethonium, or due to cardiac vagal reflexes.

Robinul (glycopyrrolate)–Neostigmine injection, is the first ready-made reversal mixture. Robinul–Neostigmine injection is associated with less tachycardia and better protection against the subsequent cholinergic effect of neostigmine methylsulphate than a mixture of atropine and neostigmine methylsulphate.

ALBERT WAESCHLE

P.O. Box 19,
123–125 Old Christchurch Road,
Bournemouth, Dorset BH1 1EX
Tel. 0202-290502/557513; Fax 0202-299683
Sales and Marketing Manager: Allan Attwood

Albert Waeschle is a wholly owned British company, acting as sole or main agent for a number of international companies in the healthcare industry, including Heine and Martin of Germany.

Products from Heine and Martin include a full range of laryngoscopes, surgical and anaesthetic hand-held instrumentation and anaesthetic sundries. Cardioline ECG machines, Bosch sphygmomanometers, pulse meters, TENS units and oscillotonometers are also in the product range.

ALLERGAN PHARMACEUTICALS

Coronation Road, High Wycombe,
Buckinghamshire HP12 3SH
Tel. 0494-427029; Fax 0494-473593
Marketing Manager: Peter Woodward

Allergan has three divisions. Allergan Pharmaceuticals supplies ethical prescription medicines primarily for use by hospital ophthalmologists. Betagan (levobunolol hydrochloride) and Propine (dipivefrine hydrochloride eyedrops) are used widely for the treatment of open angle glaucoma. Pred Forte (prednisolone acetate) is a steroid product for the treatment of ocular inflammation. Lacri-Lube (petrolatum mineral oil) was developed by Allergan for use in the night-long control of dry eye conditions and is also suitable for the protection of the cornea during general anaesthesia, without the need for frequent applications.

The other divisions of Allergan include Allergan Medical Optics who supplies intraocular lenses while Allergan Optical is a market leader in the field of contact lenses and contact lens solution.

AMBU INTERNATIONAL (U.K.) LTD

Charlton Road, Midsomer Norton,
Bath BA3 4DR
Tel. 0761-416868; Fax 0761-419429
Sales Manager: Jon Hamer

Recent updates include the Cardio Pump, developed to fulfil the needs of the active compression–decompression technique of CPR. A full range of bag resuscitators including SPUR (single patient use), silicone and the original twin-walled version is available in both adult and child sizes.

A range of bracketed containers provide storage suitable for both vehicle and wall locations.

The Ambu Matic automatic resuscitator has a wide range of functions making it suitable for both small children and adults. It is particularly relevant to patient transport and can be rail mounted.

A defib version of the popular Ambu Man is now available.

Ambu products are on display at the premises in Midsomer Norton. Advance notice of a visit is appreciated.

ANDERSEN PRODUCTS LTD

Davy Road, Gorse Lane Industrial
Estate, Clacton-on-Sea CO15 4XA
Tel. 0255-428328; Fax 0255-222987
Office Administrator: Vina Finlayson

HW Andersen Products has for many years supplied superior wound drains and reasonably priced fluid collection systems. The company has an excellent range of silicone drains and free samples are available on request.

Also available are the new vented gas sterilizers, both manual and automatic, with extraction unit and purge system.

ANETIC AID LTD

Wells Road, Guiseley,
West Yorkshire LS20 9AE
Tel. 0943-878647/873081; Fax 0943-870455
Director: Thomas Brady

Anetic Aid Ltd manufactures and supplies the APT Mark 3 pneumatic tourniquet inflation unit. Operating from a compressed air supply of either 4 or 7 bar, this double channel unit is ideally suited for regionalized anaesthetic block procedures including Biers block. Cuff pressures can be preselected and inflation time is recorded automatically, each channel having its own dedicated timer.

Also available is a full range of tourniquet cuffs, the Rhys Davies Exanguinator and an automatic timing unit for use with existing dual channel inflation machines.

The company also supplies a range of hospital furniture and diagnostic instruments.

ASSOCIATION OF BRITISH HEALTH-CARE INDUSTRIES

Consort House, 26/28 Queensway,
London W2 3RX
Tel. 071-221 4612; Fax 071-229 4708
Press and Marketing Officer: Richard Geller

The Association of British Health-Care Industries (ABHI) is the trade association for the U.K. healthcare industry. It is an independent non-profit making body run by a small team with expertise in commercial and regulatory affairs and acts as an effective communication channel for all those involved in healthcare in the U.K. and overseas.

The ABHI has a membership of over 200 British companies covering the breadth of Britain's capabilities in the provision of healthcare. The members range from medical equipment manufacturers and pharmaceutical companies to consultants, architects and healthcare planners.

ASTRA PHARMACEUTICALS LTD

Home Park, Kings Langley,
Hertfordshire WD4 8DH
Tel. 0923-266191; Fax 0923-260431

Astra has been the world leader in local anaesthetics for 40 years, supplying some of the best known products on the market such as Xylocaine, Marcain (bupivacaine) and Citanest (prilocaine). Each product comes in a wide range of presentations, covering almost every possible application from dentistry to obstetrics. Astra are also continually active in research and development. New projects based on known, as well as completely new mechanisms of pain relief are underway with special attention to spinal anaesthesia.

AVL MEDICAL INSTRUMENTS U.K. LTD

Unit 24, Whitebridge Industrial Estate,
Whitebridge Lane, Stone,
Staffordshire ST15 8LQ
Tel. 0785-815987; Fax 0785-816863
Sales Manager: Len Jones

AVL Medical Instruments U.K. Ltd is a wholly-owned subsidiary of AVL AG, Schaffhausen, Switzerland, a worldwide company specializing in the design and manufacture of blood-gas, ISE and associated analysers. A comprehensive range of blood-gas analysers is available to cover both specification and budget. The ISE analyser range includes seven distinct instruments featuring long-life disposable electrodes which AVL manufactures for its own analysers and supplies to many other leading analytical instrument manufacturers. AVL has 86 worldwide offices to support the product range at local level assuring the user of immediate response to technical and application enquiries.

B BRAUN MEDICAL LTD

Braun House, 13/14 Farmbrough Close, Stocklake, Aylesbury,
Buckinghamshire HP20 1DQ
Tel. 0296-393900; Fax 0296-435714
Divisional Manager: Malcolm White

B Braun Medical Ltd has been a leading supplier to the critical care market in the U.K. for over 12 years.

The Hospital Products Division offers a range of single-use products for critical care areas which include: Stimuplex S and needles—nerve stimulator set and cannula; Perifix minisets—extradural sets; Vasofix—i.v. cannula; Ureofix 500—closed urine measuring system; Intrafix B—i.v. administration set; Sangofix—blood administration set.

Infusion equipment include a volumetric pump, the Infusomat Secura, and the syringe pumps, Perfusor Secura FT and P as well as the Perfusor M/ME ambulatory pumps. The Dianet Patient Data Collection computer interface system can also be linked to the new Infucommand for use in PCA.

The Cardio Medical Division supplies thermodilution and wedge pressure products with the introduction of Eledyn and the Corodyn range of balloon-tipped catheters. A range of disposable pressure transducer kits is also available.

BARD LTD

Forest House, Brighton Road,
Crawley, West Sussex RH11 9BP
Tel. 0293-527888; Fax 0293-552428
Anaesthesia Contact: Anna Porter

Bard Ltd provides a range of patient controlled analgesia (PCA) pumps. The PCA systems deliver i.v. analgesia to the patient on demand for both acute and chronic relief of pain. The range includes the Bard PCA, PCA 1 and the Ambulatory PCA pump—all have a variety of features that can be utilized depending upon the hospital acute pain service requirements. A full range of accessories are available, as is a comprehensive in-service training programme.

A revolutionary multi-drug delivery system for use in operating theatres and intensive care is also available from Bard. The InfusO.R. pump is automatically programmed for infusion of a specific drug with the simple application of one of the magnetically encoded "smart labels". The smart label system converts the InfusO.R. into a specific delivery system for a particular i.v. agent. It eliminates the need for complex calculation and ensures an accurate infusion regimen, which can reduce the risk of improper delivery.

BAXTER HEALTHCARE LTD

Wallingford Road, Compton,
Newbury, Berkshire RG16 0QW
Tel. 0635-200020; Fax 0635-578800
Product Manager (Critical Care):
Mark van Rossum

Baxter Healthcare has three groups developing products for use in anaesthetics and critical care.

Flow Control: The Flo-Gard 6200 volumetric infusion pump offers all the features of today's technology utilizing stand administration sets. The Flo-Gard 200 syringe pump allows low volumes to be delivered accurately and safely.

Critical Care: Edwards Critical Care Division supplies Swan-Ganz thermodilution catheters, including a mixed venous oxygen catheter and a right heart ejection fraction catheter. Cardiac output computers, introducer trays and closed injectable systems to accompany these catheters are also supplied, in addition to a range of disposable pressure transducer kits and VAMP—a needleless blood sampling system.

Patient Controlled Analgesia: The Baxter PCA Infusor is a disposable system for managing both postoperative acute and chronic pain. The Infusor enables hospitals to set up pain services without the need to purchase large numbers of PCA machines.

BECTON DICKINSON

Between Towns Road, Cowley,
Oxford OX4 3LY
Tel. 0865-748844; Fax 0865-781503
Division Manager: Keith Elsey

Becton Dickinson is a leading manufacturer of disposable medical products. Within the B-D organization there are four divisions of which Medical is one of the largest. Medical is divided into two divisions, Supply and Technique. Supply Division's main emphasis is hypodermic products, which include the market leading Plastipak syringes and Microlance 3 needles. The new range of clear barrel syringes offers optimum visualization, whilst the superior technology of Microlance 3 needles ensures the maximum patient comfort. Other product ranges include the Tru-Touch vinyl examination gloves, the E-Z Scrub disposable brushes, drapes and face masks.

The Technique Division has a range of disposable products. B-D's peripheral i.v. cannula, Insyte, offers consistently high flow rates and excellent *in situ* performance. The range of Yale spinal needles has been expanded by the introduction of Whitacre atraumatic 22-gauge and 25-gauge needles and the new Whitacre 27-gauge is the finest pencil point available anywhere.

B-D offers also single and multi-lumen central venous catheters in adult and paediatric sizes.

BIOMEDICAL SENSORS LTD

P.O. Box 88, 5 Manor Court Yard,
Hughendon Avenue, High Wycombe,
Buckinghamshire HP13 5RE
Tel. 0494-446651; Fax 0494-534489
Managing Director: Roy Johnson
Marketing Manager: Roger Pamment

Biomedical Sensors Ltd specializes in the development, manufacture and marketing of continuous blood-gas monitoring systems for use within critical care and surgical departments of healthcare establishments.

Individual systems are available for the monitoring of neonatal patients and for general intensive care admissions, while a multi-parameter monitoring system addresses the particular needs of cardiopulmonary bypass surgery. Additional further development of the multiparameter system for intravascular use may also provide a valuable clinical tool for intensive care.

Biomedical Sensors facilities incorporate all manufacturing, marketing, development, and administrative resource in High Wycombe, U.K. The company forms part of the Pfizer Hospital Products Group, a major international healthcare organization.

While continually seeking product innovation, Biomedical Sensors vigorously maintains a commitment to quality in all areas, ensuring that products meet high standards of design, manufacture and safety, to contribute towards improved patient care.

BLEASE MEDICAL EQUIPMENT

Deansway, Chesham,
Buckinghamshire HP5 2NX
Tel. 0494-784422; Fax 0494-791497
Sales Director: M. E. Cadman

Blease Medical Equipment continues to supply its wide range of ventilators for theatre. The range of ICU ventilators, from the Brompton to the 9100s covers all needs. The company has now over 10 000 Manleys in daily use worldwide.

The company prides itself in the design of easy to operate ventilators and anaesthetic trolleys. The cost of ownership has been reduced in that maintenance is simple (in most cases carried out by highly trained service engineers) and the machines are built to last.

The company's anaesthetic trolleys have been designed with flexibility in mind.

The company also carries a wide range of oxygen therapy flowmeter, gauge units and a range of laryngoscopes, including fibreoptics. Blease carries a complete range of suction to suit all hospitals needs.

BPR MEDICAL

17 St John Street, Mansfield,
Nottinghamshire NG18 1QJ
Tel. 0623-28281; Fax 0623-421163
Managing & Marketing Director:
David M. Baker

BPR Medical is the marketing, sales and service support division of Arcomed Ag—a Swiss manufacturer of volumetric infusion pumps. The company offers two volumetric pumps designed to meet most i.v. therapy requirements—the Volumed Vp2002 and the Volumed Vp4000. The Volumed Vp2002 provides excellent short- and long-term volumetric accuracy for application of cytotoxic drugs and i.v. anaesthetics with constant large displays of rate, volume to be infused and actual volume infused. The Volumed Vp4000 is ideal for less critical drug therapy, fluid infusions, blood, etc. It has a unique memory capability of the previous eight infusions and last four alarms.

The company also designs and manufactures innovative control equipment for use primarily in neonatal intensive care respiratory therapy. The design team is extremely keen to work closely with consultants to develop and market their ideas on a joint venture basis.

BRÜEL & KJAER

Harrow Weald Lodge,
92 Uxbridge Road,
Harrow, Middlesex HA3 6BZ
Tel. 081-954 2366; Fax 081-954 9504
Medical Sales Manager: Dennis Lewis

Brüel & Kjaer is a Danish company with worldwide subsidiaries which produce medical equipment. Bruel & Kjaer has developed ultrasound scanners for use in radiology, urology, surgery, neurosurgery, obstetrics and gynaecology.

The 1304 anaesthetic gas monitor is a new multi-gas analyser with built-in pulse oximeter. The monitor provides real time information on inspired and expired concentrations of oxygen, carbon dioxide, nitrous oxide and inhalation anaesthetic agents. The 1304 uses a new method of gas detection called photoacoustic spectroscopy. This technique has the advantage of being fast, accurate and stable. Oxygen is measured using the magnetoacoustic technique. The 1304 is extremely cost effective, there are no consumable parts and it rarely requires calibration.

BUTTERWORTH–HEINEMANN LTD

Linacre House, Jordan Hill,
Oxford OX2 8DP
Tel. 0865-310366; Fax 0865-311279
Sales Product Manager: Judy Chappell

Butterworth–Heinemann is a major international publisher of surgical and medical books and journals. In the anaesthetic area the company publishes *Journal of Clinical Anaesthesia*, a bi-monthly journal (Editor-in Chief Richard J. Kitz, Harvard Medical School, free sample copies of the journal are available on request).

Among Butterworth–Heinemann's major book titles are: *General Anaesthesia*, 5th Edn, ed. J. F. Nunn *et al*; *Drugs in Anaesthetic Practice*, 7th Edn, ed. M. D. Vickers *et al*; *Pharmacokinetics for Anaesthesia*, C. J. Hull; *Intensive Care Manual*, 3rd Edn, T. E. Oh; *Nunn's Applied Respiratory Physiology*, 4th Edn, J. F. Nunn; *Lee's Synopsis of Anaesthesia*, 11th Edn, ed. R. S. Atkinson *et al*; *Standards of Care in Anaesthesia*, T. H. Taylor, D. R. Goldhill; *Anaphylectic Reactions in Anaesthesia and Intensive Care*, ed. J. H. Levy; *Case Presentations in Anaesthesia and Intensive Care*, ed. K. J. Power; *MCQs in Anaesthesia: Basic Sciences*, ed. B. Kumar; *Problems in Anaesthesia: Life Threatening Problems*, A. Sutcliffe; *Techniques in Extracorporeal Circulation*, 3rd Edn, ed. P. H. Kay; *Psychology, Psychiatry and Chronic Pain*, ed. S. P. Tyer. The company also produces pharmacokinetic software which will run on all IBM compatible computers.

CAMBMAC INSTRUMENTS LTD

Ethicare House, Pembroke Avenue,
Waterbeach, Cambridge CB5 9PY
Tel. 0223-441144; Fax 0223-441044
Sales and Marketing Director: Nick Willys

Cambmac Instruments, based in Cambridge, is the leading supplier of ECG electrodes in the U.K., and the fastest-growing supplier of ostomy products.

The ECG electrodes include the Medicotest Blue Sensor ECG disposable electrodes for monitoring, neonatal/paediatric and diagnostic use.

Ostomy products include Dansac ileostomy and colostomy pouches, standard and mini; sterile drainable pouches and irrigation sets.

CARDIAC RECORDERS INTERNATIONAL PLC

Unit 2, Watermill Business Centre,
Edison Road, Millmarsh Lane,
Enfield, London EN3 7XF.
Tel. 081-364 7000; Fax 081-364 7716
Sales and Marketing Manager: Eric King

Cardiac Recorders manufactures and supplies electromedical equipment.

The company's range of equipment includes the CR5000, CR6000 and CR7000 series range of monitors offering a range of parameters. Cardiac Recorders is the U.K. distributor of ESAOTE Biomedica products and ZOLL, offering their PD500, PD1200 and PD1400 defibrillators.

Cardiac Recorder's range of defibrillators includes the fully portable combined defibrillator and monitor (CR272). The combined defibrillator, monitor and recorder (CR26) has large screen display of ECG, heart rate and discharge energy level, internal and external defibrillation, joules indicator on paddle and flush touch controls.

CARDIOKINETICS LTD

2 Kansas Avenue, Salford M5 2GL
Tel. 061-872 8287; Fax 061-848 7916
Sales Administration Manager: S. L. Turner

Cardiokinetics Ltd is the exclusive U.K. distribution for many well known medical names, such as SensorMedics (Gould), Schiller and Metro.

SensorMedics will be adding a number of exciting products to its range this year including a new B × B gas analysis system and two new pulmonary function systems, one designed specifically around the neonatal/paediatric application.

Schiller has developed a combined ECG recorder with oxygen saturation, a combined ECG recorder with non-invasive blood pressure, an economy version of the 12-channel electro-cardiograph recorder and a bedside monitor utilizing the latest liquid crystal flat screen technology.

From Metro a new range called Metroflex, the ultimate in flexibility, will allow a cart to be built to any specification from a low profile cart to a high profile anaesthetic cart.

CENTRAL MEDICAL SUPPLIES LTD

CMS House, Town Yard Ind. Estate,
Station Street, Leek,
Staffordshire ST13 8BP
Tel. 0538-399541; Fax 0538-399572
Managing Director: P. A. Champ

Central Medical Supplies is a private company, succeeding Kanthal Medical Heating in the supply of all Kanthal patient warming mattreses in the U.K.

Kanthal operating table mattresses are now used throughout the U.K. and are much preferred to water or air-based systems.

Central Medical Supplies is also the U.K. distributor for Action Products' range of pressure-sore prevention pads for the operating theatre and ITU, and supplies Ellab temperature monitoring equipment.

CHILDERHOUSE MEDICAL

310A Upper Richmond Road West,
East Sheen, London SW14 7JN
Tel. 081-876 6040 (4078); Fax 081-876 4078
Manager: E. Petchell

Childerhouse Medical is a well established distributor of anaesthetic sundries, serving all sectors in the U.K. and throughout the world.

The company covers a wide range of non-disposable products such as bronchial and tracheal tubes and connectors, facemasks, conventional and fibrelight laryngoscopes, corrugated and antistatic tubing, rebreathing bags, and airways.

CHURCHILL LIVINGSTONE

Robert Stevenson House,
1–3 Baxter's Place, Leith Walk,
Edinburgh EH1 3AF
Tel. 031-556 2424; Fax 031-558 1278
Sales Promotion Manager: Jane Grounsell

Churchill Livingstone is the U.K.'s largest health sciences publisher offering a wide range of books and journals, ideally suited to the needs of anaesthetists in training and practice.

These include: *Textbook of Anaesthesia*, 2nd edn, ed. A. R. Aitkenhead and Graham Smith; *Anaesthesia Review—9*, ed. L. Kaufman; *Recent Advances in Anaesthesia and Analgesia—17*, ed. R. S. Atkinson and A. P. Adams; *Clinical Anaesthetic Pharmacology*, ed. J. W. Dundee, R. S. J. Clarke, W. McCaughey; *Vascular Anesthesia* and *Thoracic Anesthesia*, ed. J. A. Kaplan; *Adult Respiratory Distress Syndrome*, ed. A. Artigas, F. Lemaire; *Handbook of Anaesthesia and Co-existing Disease*, 2nd Edn, ed. R. K. Stoelting, S. F. Dierdorf and R. L. McCammon; *Hazards and Complications of Anaesthesia*, ed. T. H. Taylor and E. Major.

Journals include: *Current Anaesthesia and Critical Care* Volume 4, four issues per volume. A unique international review journal devoted to the current practice of anaesthesia and critical care. An invaluable source of information to trainee and qualified anaesthetists at all stages of their careers. *International Journal of Obstetric Anesthesia* Volume 2, four issues per volume. The Official Journal of the Obstetric Anaesthetists' Association. The first journal devoted exclusively to original research in obstetric anaesthesia, analgesia and related topics aims to improve communication worldwide in this important and expanding area. *Intensive and Critical Care Nursing* Volume 9, four issues per volume. The Official Journal of the British Association of Critical Care Nurses. Promotes excellence of care of critically ill patients by specialist nurses and their professional colleagues. Provides an international and interdisciplinary forum for publication, dissemination and exchange of research findings, experience and ideas.

CIBA CORNING DIAGNOSTICS LTD

Colchester Road, Halstead, Essex
CO9 2DX
Tel. 0787-474742; 0787-475088
Product Manager: Martyn Toms

A comprehensive range of Critical Care products is available from Ciba Corning Diagnostics. These include analysers for blood-gas, blood electrolytes, co-oximetry and coagulation.

The 200 series automated blood-gas analysers employ maintenance-free electrode sensors (Ready Sensors) and include complete support packages of quality control materials, sampling devices and data management systems. Cost effective blood-gas analysis for the low throughput user is available via the model 238. Other facilities available include remote monitoring and linkage to a co-oximeter for oxygen dissociation curve analysis. Information regarding tissue oxygenation using the blood-gas and co-oximeter is available via an automated Swan Ganz procedure to allow oxygen supply, oxygen extraction ratio and shunt equations to be produced.

Blood electrolyte analysers are available for automated measurement of Na, K, Cl, pH, Ca and Li in whole blood, serum, plasma or urine. Results are available within 40 s and when combined with an optional autosampler provides high productivity for routine electrolyte analysis.

Patient-side APTT and PT results can be obtained in seconds using the 512 coagulation monitor. The 512 is designed for the operating room, ICU and other areas where fast and reliable coagulation results are required.

Rapid-Lyte samplers contain a reduced dry heparin formula resulting in no blood clotting or sample dilution errors. Calcium binding is also eliminated in the blood sample resulting in accurate electrolyte measurements. Only one blood sample is required to measure blood gases, pH and selected electrolytes. A complete range of arterial blood samplers is available for pH/blood gas and electrolyte analysis (adult and paediatric).

CIBA-GEIGY PHARMACEUTICALS

Wimblehurst Road, Horsham,
West Sussex RH12 4AB
Tel. 0403-272827; Fax 0403-56643
Therapeutic Area Operations Manager: Mike Crooks

For postoperative pain relief following major surgery as well as day-case procedures, there is a wide range of Voltarol formulations available: Voltarol ampoules 75 mg/3 ml—1–2 i.m. injections daily for a maximum of 2 days; Voltarol suppositories 100 mg once daily; if preferred to injection. Voltarol dispersible 46.5 mg tid—for rapid absorption and for patients who cannot take tablets.

COBE LABORATORIES LTD

Athena 2, Olympus Business Park,
Quedgeley, Gloucester
GL2 6NF
Tel. 0452-722070; Fax 0452-720172
Cardiovascular Sales Manager:
Stephen Pope
Customer Service Representative: Josie Fleet

Cobe Laboratories Ltd is a medical speciality company concerned with all aspects of extracorporeal circuitry and equipment. The company is a world market leader in flat sheet membrane oxygenator technology with the CML (Cobe membrane lung), and CML Excel, CML Ultra, and variable Prime CML cover the total patient range.

Cobe personalized perfusion products are manufactured in a new facility at Gloucester. All styles and types of extracorporeal circuit and monitoring lines can be designed for the perfusion and critical care arena.

Autotransfusion can be accomplished with the Cobe "BRAT" system and haemoconcentration. In addition, Cobe offers cardioplegia delivery systems and topical cooling devices for open heart surgery.

Other divisions of cobe Laboratories are concerned with apheresis, blood banking, and haemodialysis.

CODAN

Eastheath Avenue, Workingham,
Berkshire RG11 2PR
Tel. 0734-783663; Fax 0734-776274
General Manager: E. Bay-Andersen

Codan is one of Europe's largest manufacturers of i.v. disposable equipment with manufacturing plants based in Lensahn, Germany, Portugal, Denmark and the U.S.A. Codan is a specialist in this area with over 30 years experience in producing high quality products at competitive prices.

Codan Ltd entered the U.K. market as a direct supplier early in 1987.

Codan's wide range of products include colour-coded new technology DH approved long and standard length solution sets, a newly developed blood set, a full range of blood, solution and in-line burettes and secondary medication set for administration of intermittent i.v. admixtures i.e. metronidazole. Cassette type air venting needle, incorporating a non-return valve and non-wettable bacterial filter. Full range of extension sets, microbore, standard and widebore. There are also inert and light sensitive sets and a 0.2 Micron Final Filter. Codan offers also the facility to produce specialist custom-built sets if required.

A range of protective clothing, gowns, gloves, prep mats, armsleeves and goggles specifically designed for staff preparing cytotoxic drugs are also available.

COLGATE MEDICAL

1 Fairacres Estate, Dedworth Road,
Windsor, Berkshire
SL4 4LE
Tel. 0753-860378; Fax 0753-831137
Marketing Director: Oliver Miller
Field Sales Manager: Heather Melrose

Colgate Medical supplies the Intavent laryngeal mask. This new general purpose airway has gained wide acceptance throughout the NHS and private sector hospitals for use in routine anaesthesia. The laryngeal mask, available in six sizes in the standard range and four sizes in the new reinforced range, is specially designed for ENT, head and neck surgery and dental procedures.

The technique for using this novel airway is illustrated with a range of educational literature and visual aids obtainable from Colgate Medical.

A number of supporting products are currently being developed.

CORY BROTHERS

4 Dollis Park, Finchley,
London N3 1HG
Tel. 081-349 1081; Fax 081-349 1962
Director: Robert Sharpe

Cory Brothers supplies a range of consumable and reusable equipment including: ECG electrodes, Defib pads and the Venigard IV protection and stabilization device.

The company also supplies anaesthetic equipment including: Cory Bains valve. Coaxial anaesthetic circuits, ventilator circuits—adult and infant. Hygroscopic condenser humidifiers (HMEs), filters and combined units for long and short procedures. Bullard intubating laryngoscope is a fibreoptic scope for difficult and routine cases.

CRITIKON

The Braccans,
London Road, Bracknell,
Berkshire RG12 3AT
Tel. 0344-864090; Fax 0344-864091
European Business Director: Graham Sethna

Critikon manufactures a wide range of products for use in the critical care and non-critical care environment. The product range includes Jelco* i.v. catheters, Dinamap* non-invasive blood pressure monitors, Oxyshuttle® pulse oximeters and Protectiv* i.v. catheter safety system.

Recent product introductions include the Dinamap* plus physiological monitor which is a portable device for the monitoring of ECG, non-invasive blood pressure, pulse oximetry, invasive pressure and temperature.

Critikon also offers full and rapid service cover on a contract or call-out basis, and a wide range of alternative financing mechanisms for the acquisition of equipment.

*Trademark Critikon Ltd; ®Trademark SensorMedics Corp.

CROWN GRAPHIC (U.K.) LTD

Clyde Vale, Forest Hill,
London SE23 3JA
Tel. 081-699 9200 (ext. 212);
Fax 081-699 3687
Managing Director: John Davis

Crown Graphic supplies electromedical equipment including ECG/fetal monitoring chartpaper and electrodes/accessories.

DANIELS HEALTHCARE

Unit 14, Station Field Industrial
Estate, Kidlington, Oxon OX5 1JD
Tel. 08675-71841/2; Fax 0865-841869
Director: W. M. Hatton

Daniels Healthcare manufactures trolley-mounted, wall-mounted and portable anaesthetic machines, oxygen therapy flowmeters and regulators, Portapak portable oxygen inhaler, disposable Sharpsbins for the safe collection and disposal of sharps and hazardous waste.

DATASCOPE MEDICAL CO LTD

Lakeview Court, Spitfire Close,
Ermine Business Park, Huntingdon,
Cambs PE18 6XR
Tel. 0480-433477; Fax 0480-434051
General Sales Manager: Keith Barrett-Small

Datascope designs and manufactures a comprehensive range of patient monitors.

The new Passport range of transportable patient monitors provides ECG with non-invasive blood pressure, pulse oximetry, temperature and ventilatory frequency. Options include invasive blood pressure, end tidal carbon dioxide and a recorder. Passport is available with LCD or electroluminescent (EL) display. The Datascope range includes the Accutorr automatic non-invasive blood pressure monitor, which is available with pulse oximetry and a recorder.

The 3000A range of vital signs monitors and the Multinex range of respiratory gas monitors (now available with automatic agent ID) are designed to meet the monitoring needs of today's anaesthetist and can be upgraded in the hospital as requirements change. All of these monitors feature on-screen trends and interface capabilities.

DAWSON MCDONALD & DAWSON LTD

Compton Works, Ashbourne,
Derbyshire DE6 1DB
Tel. 0335-43184; Fax 0335-42540
Managing Director: J. E. Dawson

Dawson McDonald & Dawson manufactures a range of oil-free diaphragm compressors and gas circulating pumps. The 2D/351 BC VM-4, housed in a sound-reducing cabinet with a white Wareite facing, is very suitable for hospital application due to its low noise level. The principal use of this machine is in connection with the powering of ventilators. Designed to work at a pressure of 30 psig, with an output of approximately 0.5 scfm, the compressor is robustly engineered and intended for long periods of trouble-free operation.

DELANDALE LABORATORIES LTD

Delandale House, 37 Old Dover Road,
Canterbury, Kent CT1 3JF
Tel. 0227-766353; Fax 0227-470626
Managing Director: David Cockburn
Sales Manager: Paul Balmer

Delandale Laboratories Ltd produces a variety of pharmaceutical products including: Priadel, controlled release lithium carbonate tablets and Priadel Liquid for affective disorders. Dicynene 500 tablets for the control of menorrhagia. Dicynene injection for the prophylaxis and treatment of periventricular haemorrhage in low birth weight infants. Biophylline syrup and controlled release theophylline tablets for the control of bronchospasm.

DELPH MEDICAL PRODUCTS LTD

G. W. Chemicals Buildings,
Ainleys Industrial Estate,
Elland, West Yorkshire HX5 9JP
Tel. 0422-374248; Fax 0422-310060
Director: R. G. White

Delph Medical Products Ltd is a small company which manufactures a battery powered ventilator alarm unit which indicates, both audibly and visually, pressure cycling failure or excessive pressure within the patient breathing circuit. The alarm unit was introduced in December 1988 and since then it has been supplied to about 200 hospitals throughout the U.K.

Delph Medical Products also supplies oxygen monitors and alarm indicator panels for remote signalling applications.

DEVA MEDICAL ELECTRONICS

8 Jensen Court, Astmoor Industrial
Estate, Runcorn, Cheshire WA7 1SQ
Tel. 0928-565836; Fax 0928-580788
Managing Director: R. H. Betteley

Deva Medical supplies and services a complete range of electromedical equipment for hospital and home care use. This includes domicillary, ICU and emergency/transfer ventilators, temperature monitors, nebulizers, disposable ECG electrodes and oxygen analysers.

DIDECO LTD

Shiley House, 42 Thames Street,
Windsor, Berkshire SL4 1PR
Tel. 0753-857545; Fax 0753-841977
General Sales and Marketing Manager:
Jim Russell

Dideco Ltd incorporates Dideco and Stockert.

Dideco manufactures STAT (Shiley therapeutic autotransfusion system) a fully automated autologous transfusion system for use in theatre, incorporating a remote control for ease of use. Dideco also manufactures oxygenators, reservoirs, perfusion tubing and all other requirements for extracorporeal circuity for use during open heart procedures.

Stockert manufactures fully automated heart/lung machines and cardiac cannulae.

Dideco Ltd also manufactures a wide range of tracheostomy tubes, many available with disposable inner cannulae.

DRACARD

5 Commerce Way, Waddon,
Croydon CR9 4PN
Tel. 081-686 1051; Fax 081-686 3204
Director of Marketing: David Gee

Dracard has over 30 years' experience in the manufacture of charts for recording instruments and ECG machines. The recent acquisition of Dracard by The Cutting Group, a world leader in the paper conversion business since 1920, has consolidated Dracard as a leading chart supplier. Rolls, packs, sheets and circle charts can be supplied for all recording applications. Specialities include printed and perforated industrial rolls, electrocardiograph rolls, pathology and other laboratory charts.

A comprehensive range of disposable pens is available for use with most recorders, as well as skin electrodes for cardiac use, conductive gel and cream, heart rate calculators and cardiogram mounts.

DRÄGER MEDICAL LTD

The Willows, Mark Road,
Hemel Hempstead,
Hertfordshire HP2 7BW
Tel. 4444-2213542; Fax 4444-2240327
Managing Director: June Bevan

Dräger Medical Ltd is a distributor for North American Dräger who supplies Narkomed anaesthesia machines, Vitalert patient monitors and the OR Data Manager. The Narkomed line includes the Narkomed 2B and Narkomed 3 anaesthesia machines and the Narkomed 4 anaesthesia workstation. All Narkomed machines feature extensive monitoring. North American Dräger also manufactures the Vitalert stand-alone monitors with a 5-lead ECG capacity, with two channels for invasive BP and two channels for temperature.

The newest North American Dräger line is data management, represented by the OR Data Manager. The OR Data Manager allows the anaesthetist to collect patient data in the OR from the anaesthesia machine itself and also to enter data from clinical observations, patient history or other sources to provide a computerized anaesthesia record.

DU PONT PHARMACEUTICALS LTD

Avenue One, Letchworth
Garden City, Herts SG6 2HU
Tel. 0462-488200; Fax 0462-488206
Managing Director: Ann Horner
Information Manager: Janice Fuller

Du Pont Pharmaceuticals Ltd supplies a number of pharmaceutical products which may be used in perioperative or critical care situations. These include Narcane (naloxone), Hespan (hetastarch), Nubain (nalbuphine), Intropin (dopamine), Tridil (nitroglycerine), Brevibloc (esmolol).

EAST HEALTHCARE LTD

Sandy Lane West, Littlemore,
Oxford OX4 5JT
Tel. 0865-714242; Fax 0865-747249
Sales Director: T. James

East Healthcare Ltd manufactures and supplies a wide range of anaesthetic and pipeline related products for use in theatre, recovery, ICU and general wards.

These include: anaesthesia machines, vaporizers, ventilator alarms and humidifiers, suction and oxygen therapy equipment, medical rail, resuscitation trolleys and room dividers, accessories and consumables.

In addition, the company designs, manufactures and installs medical gas and vacuum pipelines.

ELCOMATIC LTD

Kirktonfield Road, Neilston,
Glasgow G78 3PL
Tel. 041-881 5825; Fax. 041-881 5828
Sales Director: Hugh H. Lang

Elcomatic Ltd has operated in the field of electromedical monitoring and instrumentation for many years. Over the last 3 years, however, it has specialized in the supply of physiological transducers which cover both venous and arterial blood pressures. The transducers (EM 750 & 751) can be supplied in the autoclavable form and are electrically compatible with most electromedical signal conditioning instrumentation providing a.c. or d.c. bridge excitation. The transducers use a silicon diaphragm with a fully active integrated strain gauge bridge diffused into the surface. The EM 751 has a thicker sensing diaphragm which incorporates a feature giving extremely high isolation and provides a higher overload pressure capability. The silicon sensing member design provides a very high linearity, accuracy and temperature stability in addition to other performance advantages such as high overload, good frequency response and low hysteresis.

ELI LILLY & CO LTD

Dextra Court, Chapel Hill,
Basingstoke, Hampshire RG21 2SY
Tel. 0256-485249; Fax 0256-485858
Medical Information Officer: Maxine Campbell

Eli Lilly manufactures Brietal sodium (methohexitone sodium) in crystalline form which is available in vials of 100 mg 10 ml^{-1}, 500 mg 50 ml^{-1}. Brietal sodium is a rapid, ultrashort-acting barbiturate for the induction of anaesthesia. It is used alone for short surgical procedures or in combination with other agents for more prolonged anaesthesia. The drug is administered i.v. in a 1% solution (10 mg ml^{-1}). The adult dose usually ranges from 5–12 ml (50–120 mg for an average of 70 mg) but should be adjusted to the needs of the individual patient. The induction dose maintains unconsciousness for approximately 5–7 min.

E MERCK PHARMACEUTICALS

Winchester Road, Four Marks, Alton,
Hampshire GU34 5HB
Tel. 0420-64011; Fax 0420-64427
Product Manager (Nutrition): S. C. Whitney

The Nutritional Division of E Merck Pharmaceuticals supplies a range of enteral feeds for tube or sip-feeding of most categories of patients requiring nutritional support together with a high quality range of nasoenteral feeding tubes—the "Silk and Corsafe" tube range—and the new Bower PEG gastrostomy and corscope feeding tubes.

Enteral feeds for patients with normal requirements include: Liquisorb 500 ml bottles (neutral tube feed, strawberry, vanilla, banana and chocolate sip feeds) and Liquisorb 200 ml tetrapaks (vanilla and strawberry sip feeds). For patients with malabsorption: Liquisorbon MCT 500 ml bottles (neutral tube feed, vanilla and strawberry sipfeeds) are available together with Triosorbon tube or sip feed in 85 g sachets. For patients with severe malabsorption and/or maldigestion: Peptisorb 500 ml bottles (neutral tube or sip feed) and Peptisorbon tube or sip feed in 83 g sachets are available. Patients with higher than normal energy/protein requirements may benefit from the newly launched high energy Liquisorb 500 ml tube feed which provides 1.5 Kcal/ml and 6 g protein/100 ml.

EME TRICOMED LTD

17 Bristol Gardens, Brighton, Sussex
BN2 5JR
Tel. 0273-609101; Fax 0273-694254
Marketing Director: Steve Foster

EME Tricomed supplies electromedical and anaesthetic equipment, including anaesthetic humidifiers and core temperature regulators, and adult, neonatal and paediatric disposable tubing. In addition, EME also supplies neonatal/paediatric and adult intensive care ventilators, paediatric nasal CPAP systems, adult and paediatric humidifier systems, single use adult and paediatric ventilator circuits, neonatal transport ventilators, oxygen/air mixer systems and pressure monitoring devices for ventilators.

ENGSTRÖM MIE LTD

Falcon Road, Sowton Industrial Estate,
Exeter, Devon EX2 7NA
Tel. 0392-431331; Fax 0392-439927
Marketing Manager: Janis Effer

Engström MIE manufactures and supplies a spectrum of products for anaesthesia, operating theatre, intensive care and special care use.

Products include anaesthetic apparatus for major operating theatre suites to induction rooms, including the EAS, Elsa, Cavendish M and Envoy+ apparatus. Engström MIE offers the Vapamasta 5 vaporizers, Carden Electrovent and Ventmasta ventilators, Jumbo Circle Absorber and a range of breathing circuits.

For intensive care use, the Engström ventilators include Erica and the more recently introduced Elvira and Elvira II systems with optional gas exchange and metabolic monitoring. The Eliza carbon dioxide analyser and nebulizer plus synchronization unit are offered to complement these products.

Engström MIE also has a comprehensive range of sundry products, including facemasks, reservoir bags, Edith HMEs, Y filters, and Durasorb and Viosorb soda lime and respiratory therapy equipment.

ERICH JAEGER U.K. LTD

Miller's House, Roman Way,
Market Harborough,
Leicestershire LE16 7PQ
Tel. 0858-433344; Fax 0858-410185
Managing Director: Graham Wheeler

Erich Jaeger U.K. Ltd is a subsidiary company of Erich Jaeger GmbH & Co KG. Erich Jaeger is a leading supplier of pulmonary function and test equipment in the U.K. and 50 countries around the world. In addition, the company supplies SleepLab equipment for analysis of sleep disorder.

The company's range of equipment allows studies such as ergometry, ergospirometry, spirometry, body plethysmography, diffusion and provocation.

FERRARIS MEDICAL LTD

26 Lea Valley Trading Estate,
Angel Road, Edmonton,
London N18 3JD
Tel. 081-807 3636; Fax 081-807 4886
Sales and Service Manager: Ms R. Linzell

Ferraris Medical Ltd, a division of Ferraris Development and Engineering Company Ltd, manufactures a complete range of original mechanical Wright respirometers and Haloscale Wright respirometers.

The company's range of electronic products includes the Magtak II and Magtrak IV respiration monitors. Ferraris Medical manufactures and markets the Wright peak flow meter and the Wright Pocket peak flow meter.

The company also makes the Watson intestinal biopsy capsule.

FISONS PLC

Coleorton Hall, Coleorton,
Leicestershire LE6 4GP
Tel. 0509-634000; Fax 0530-560330.
Marketing Manager: Keith Offord

Fisons plc, Pharmaceutical Division, Hospital Products is based at U.K. Operation Headquarters in Coleorton, Leicestershire. The company's product range covers a number of therapeutic areas including cardiology, critical care, diabetes and gastroenterology. Fisons plc is the leading supplier of heparin within the U.K. and has recently launched Dopacard (dopexamine) for the management of low cardiac output post-cardiac surgery. In addition, Fisons supplies Hyalase (hyaluronidase), dextran, Imferon (iron dextran), Hypurin (highly purified beef insulin) and PUR-IN (human insulin e.m.p.).

FREELANCE SURGICAL PROMOTIONS

60 Stapleton Road, Bristol BS5 0RB
Tel. 0272-559680; Fax 0272-559740
Contact: Robert Towler

Freelance Surgical Promotions are the U.K. agents for VBM Germany, whose product range includes the Quicktrach emergency cricothyrotomy device and the Manujet injector, for Transtracheal or bronchoscopic ventilation.

Also included are the Guedelfix airway, which incorporates a hard external bite block, a fixation site for tracheal tubes and a large easily cleaned airway. A new Tube-Inhaler allows metered dose bronchial dilators to be administered in line through the catheter mount. Autoclavable silicone catheter mounts with easily cleaned smooth bore lumens, and an extensive range of automatic tourniquets, including specific models for Biers block techniques, double outlet models for bilateral surgery, and single outlet models are ideal for the smaller department. All models can be mounted on their own stand, on a transfusion stand or on the side rail of an operating table. To complement the tourniquets a wide range of washable cuffs are available including a large conical cuff for the "problem thigh".

GB BIOMEDICAL PRODUCTS

38 Northgate, Sleaford,
Lincolnshire NG34 7DA
Tel. 0529-305584; Fax 0529-414336
Sales Manager: Ron Baker

GB Biomedical Products is Britain's only manufacturer of microaggregate blood transfusion filters. The company was awarded "Best Made in the Countryside" by the Design Council in April 1987 and is registered by the Department of Trade and Industry as quality assessed. The company's blood filters are marketed under the tradename Microsept and Wephil Paediatric. Published clinical comparative studies show them to be second to none in filtration efficiency and flow rates.

Filter spikes for multi-dose vials and the retention of toxic aerosols together with filters for extradural, infusion and chemotherapy injection, both hydrophilic and hydrophobic have recently been added to the range under the tradenames Unisafe, Epiflow and Infil-Air.

Unsterile, bulk packaged OEM products can be made available to medical manufacturing companies in possession of GMP or its equivalent in other countries. Sterile product is available ex-stock.

GEISTLICH SONS LTD

Newton Bank, Long Lane,
Chester CH2 3QZ
Tel. 0244-347534; Fax 0244-319327
Sales and Marketing Manager: D. A. Piercy

Geistlich Sons Ltd manufactures a range of parenteral nutrition solutions, antimicrobial and wound management products.

GILLETT AND SIBERT LTD

Kirktonfield Road, Neilston,
Glasgow G78 3PL
Tel. 041-881 5825; Fax 041-881 5828
Sales Director: Hugh H. Lang

Over the past 12 months the British manufacturer of light microscopes, Gillett and Sibert have undergone major reconstruction by their parent company, the Electronics company Elcomatic. The product range has been strengthened by the launch of two new series of microscopes. The Series 10 is a 10 W range of microscopes, specifically designed for laboratory and teaching applications, while the Series 20 has 20 W illumination and is especially suited for teaching and research. The new Series 20 research microscope was developed to replace the highly successful conference range and represents the ideal instrument for research applications. The optical refinement and 20 W illumination enable high quality C.C.T.V. and 35 mm camera work to be undertaken. The phase contrast and dark ground capabilities have been improved beyond that already available in the conference range.

GM INSTRUMENTS LTD

Unit 6, Ashgrove,
Ashgrove Road,
Kilwinning KA13 6PU
Tel. 0294-54664; Fax 0294-51154
Sales Director: E. W. Greig

Mercury designs and manufactures a range of electrospirometers, pneumotachographs and pressure transducers in the U.K., along with other specialized respiratory and industrial measurement instrumentation.

GRASEBY MEDICAL LTD

Colonial Way, Watford WD2 4LG
Tel. 0923-246434; Fax 0923-31595
Sales and Marketing Manager: J. B. Parker

Graseby Medical has achieved a worldwide reputation for the high quality and reliability of its critical care equipment, and recognition for its after sales service to customers.

Leaders in the field of ambulatory and bedside syringe pumps, patient-controlled analgesia systems and respiration monitoring, the company has extended its product range with the addition of patient monitoring equipment, measuring ECG, respiration, temperature and blood pressure (invasive and non-invasive).

Graseby Medical also sells electrical safety testers which are recognized as the approved standard for testing of equipment by manufacturers, and hospital engineers.

HAEMONETICS (U.K.) LTD

Deacon House, Seacroft Avenue,
Leeds LS14 6JD
Tel. 0532-737711; Fax 0532-734055
Marketing Manager: Tom Ford

Haemonetics is a world leader in the development of blood processing equipment and relative disposables. The company's activities encompass three principal areas: automated plasma collection, surgical blood salvage and blood component therapy. The range of Haemonetics Cell Savers enables the surgical specialities (A&E, cardiac, vascular, orthopaedic, obstetrics/gynaecology and genitourinary) to recover efficiently and safely intraoperative and postoperative shed blood for re-infusion to the same patient.

HAMILTON (G.B.) LTD

Parkgate House, Broomhill Road,
London SW18 4JQ
Tel. 081-871 5124; Fax 081-874 6010
Managing Director: L. Hewitt

Hamilton (G.B.) Ltd supplies intensive care ventilators.

HARCOURT BRACE JOVANOVICH LTD

Academic House,
24–28 Oval Road,
London NW1 7DX
Tel. 071-267 4466; Fax 071-485 4752/071-482 2293

Harcourt Brace Jovanovich is the world's leading international medical publisher, providing an extensive range of clinical books and journals under the imprints W. B. Saunders, Baillière Tindall and Academic Press.

Our more recent anaesthesia titles include: the third edition of *Ward's Anaesthetic Equipment* by Davey and co-workers (0-7020-1435-4) and the *Handbook of Percutaneous Central Venous Catheterisation, 2nd edn.* (0-7020-1539-3) from Rosen and co-workers; *A Practice of Anesthesia for Infants and Children*, 2nd Edn, by Cote (0-7216-3198-3); *Atlas of Regional Anaesthesia* by Brown (0-7216-3177-0); and *The Effect on the Baby of Maternal Analgesia and Anaesthesia*, by Reynolds (0-7020-1574-1).

Academic Press publishes the international journal, *Anaesthesia* (ISSN: 0300-2409), for the Association of Anaesthetists of Great Britain and Ireland.

Baillière's International Practice and Research in Anaesthesiology, is a series of up-to-date reviews on the latest developments and techniques in anaesthesia. Edited and written by an international team of experts, each issue covers a single topic. There are four issues per year (ISSN: 0950-3501).

HAWKSLEY AND SONS LTD

Marlborough Road, Lancing,
West Sussex BN15 8TN
Tel. 0903-752815; Fax 0903-766050
Managing Director: John A. Dinning

Hawksley and Sons Ltd supplies ripple heat hypo/hyperthermia systems for patient temperature control and pressure sore prevention in the operating theatre and intensive care. These systems are unique in not only providing temperature control from 6 °C to 40 °C but also using a double cell mattress with alternating pressure to prevent pressure sore development during long operations or in intensive care. Temperature monitors including probes are also integral with the equipment. Sphygmomanometers for general use are supplied and are imported from the W. A. Baum Co. Inc., New York, and the Hawksley Random Zero sphygmomanometer as used in many hypertension studies is considered the world standard for blood pressure measurement. In addition, Hawksley have laboratory products for blood analysis including microhaematocrit centrifuges and other microcentrifuges, haemoglobinometers and haemocytometers and counting chambers.

Hawksley also supplies particle counting equipment for analysis of airborne and liquid particles in clean rooms and clean processes. These can be used in environmentally controlled operating theatres where particulate matter and contaminants are to be counted.

HENLEYS MEDICAL SUPPLIES LTD

Brownfields, Welwyn Garden City,
Hertfordshire AL7 1AN
Tel. 0707-333164; Fax 0707-334795

Henleys supplies TENS units and accessories, as well as a full range of ECG cables, leads and electrodes, all oxygen therapy products, from the patient to the ventilator, oxygen hoods for the neonate, oxygen analysers and monitors for use with oxygen or nitrous oxide, galvanic or polarographic cells, nebulizers and humidifiers. A complete range of accessories from the simple 22 mm adaptor to magnetic PEEP valves, IMV/CPAP etc. are also available.

HEWLETT–PACKARD LTD

Customer Information Centre,
Hewlett–Packard Ltd, Cain Road,
Bracknell, Berkshire RG12 1HN
Tel. 0344-369369; Fax 0344-363344

Hewlett–Packard supplies a variety of electromedical equipment and information systems for patient and perinatal monitoring, resuscitation and diagnosis. These include: patient monitoring for ITU/CCU/theatres, central stations for ITU/CCU, arrhythmia systems, beside monitors with comprehensive patient data management capability and integrated patient record systems such as CareVue.

Perinatal monitoring—vital sign monitors for special care baby units, transcutaneous PO_2 fetal monitors for antenatal, labour and delivery departments.

Resuscitation—a wide range of defibrillator/monitors for trolley or portable use.

Diagnostics—ECG recording (Hewlett–Packard PageWriter cardiograph), exercise testing systems using the Hewlett–Packard PageWriter cardiograph, ECG data management systems, catheterization laboratory recording systems, catheterization holter systems, laboratory computer systems, real time phase array ultrasound imaging systems for echocardiography, radiology and obstetrics.

HG WALLACE LTD

Whitehall Road, Colchester,
Essex CO2 8JH
Tel. 0206-795133; Fax 0206-792722
Marketing Assistant: James Hibbins

HG Wallace Ltd is a British manufacturer of high quality intravascular devices. Recently the Wallace Y-Can has become the cannula of choice for induction of anaesthesia. Y-Can is now available in larger sizes which, when used in conjunction with the Wallace converter, provide a bloodless technique for infusion with access for intermittent injections or a second infusion.

The same standards of quality and unique design apply also to Wallace IV Cradles for temporary limb immobilization in i.v. therapy and Wallace internal jugular cannulae with a patented protective sleeve to avoid contamination on insertion and patented Flexihub hub to control the escape of blood and prevent entry of air.

HG Wallace Ltd is a member of the Smiths Industries Medical Systems group of companies. See entry under Medical-Assist Ltd for exclusive U.K. distributor.

HOECHST U.K. LTD

Hoechst House, Salisbury Road,
Hounslow, Middlesex TW4 6JH
Tel. 081-570 7712; Fax 081-577 1854

As a research-intensive international corporation and pioneer of many medical breakthroughs, Hoechst is committed to the prevention and cure of disease throughout the world.

Hoechst is a supplier of Haemaccel (polygeline, degraded and modified gelatin), Streptase (streptokinase) and Lasix (frusemide).

HUNTLEIGH HEALTHCARE

310–312 Dallow Road, Luton,
Bedfordshire LU1 1SS
Tel. 0582-413104; Fax 0582-459100
U.K. Sales Manager: David Zacks

Huntleigh Healthcare manufactures mattresses for the prevention of pressure sores, intermittent compression devices for the treatment of vascular and lymphatic problems and a range of non-invasive diagnostic and monitoring equipment for cardiovascular and obstetric medicine.

With world renowned products such as the Nimbus Dynamic Flotation System, Flowtron Intermittent Compression including Flowtron DVT and Dopplex pocket Dopplers, Huntleigh Healthcare has a reputation for quality, reliability and innovation.

ICI PHARMACEUTICALS (U.K.)

Kings Court, Water Lane, Wilmslow,
Cheshire SK9 5AZ
Tel. 0625-535999
Product Manager: Graham Cox

The Chairman of ICI announced on November 18, 1992 that the Company would be divided into two separate operating units from January 1, 1993. The division involves the hiving off of the Company's bioscience interests into a new, wholly owned subsidiary which will be called Zeneca Ltd. The new bioscience company will comprise ICI's existing pharmaceuticals, agrochemicals, seeds and specialties businesses; the pharmaceuticals business will be known internationally as Zeneca Pharmaceuticals.

In the U.K., there will continue to be two trading operations. ICI Pharmaceuticals (U.K.) will operate as Zeneca Pharma while Stuart Pharmaceuticals will retain its current identity. Zeneca Pharmaceuticals will start 1993 by adding to the clinical success of relatively new products such as Zestril, Diprivan and Zoladex with approximately 20 new products in development in the areas of cancer, cardiovascular medicine, asthma, anti-infectives and CNS disorders, products on which Zeneca Pharmaceuticals will build its future.

INSTRUMENTATION LABORATORY (U.K.) LTD

Kelvin Close, Birchwood, Warrington,
Cheshire WA3 7PB
Tel. 0925-810141 (ext. 224);
Fax 0925-826708
Sales Manager: Brian Lewin

Instrumentation Laboratory (U.K.) Ltd is a leading supplier of analytical monitoring equipment to intensive care units, special care baby units, anaesthetic departments, clinical chemistry and haematology laboratories

Products include: blood-gas analysers (including data storage facilities), with and without haematocrit, sodium, potassium and calcium measurement. Co-oximeter for measurement of haemoglobin, carboxy-, met- and oxyhaemoglobin (can be linked to blood-gas analysers for a large range of derived parameters). Blood-gas quality control materials. Whole blood sodium/potassium analysers and flame photometers for sodium, potassium and lithium.

INTEGRATED MEDICAL SYSTEMS LTD

75 Busbridge Lane,
Godalming,
Surrey GU7 1QQ
Tel. 04834-24011
Senior Programmer: Scott Reynolds

IMS specializes in high quality software products for the practising anaesthetist in the international market. Principal among these products is the unique databasing system for automatic patient data acquisition, compilation and long term storage of complete anaesthetic records marketed as the ARC system by S&W Vickers Ltd. The records are stored on an optical disc using a proprietory operating system permitting maximum utilization of this high density medium. Theatre management and anaesthetic audit reports are some of the many outputs of the system. A billing module for private practice is available either as an add on or as a stand-alone product for the individual in either solo or group practice.

INTERNATIONAL MEDICATION SYSTEMS, (U.K.) LTD

11 Royal Oak Way South, Daventry
Northamptonshire NN11 5PJ
Tel. 0327-703231; Fax 0327-72478
Director of Marketing: K. J. Reynolds

IMS (U.K.) Ltd is the international arm of Californian based International Medication Systems Ltd which manufactures and sells innovative disposable drug delivery systems, medication transfer and mixing devices, and injectable non-proprietary pharmaceutical products.

Products include: the widely used Min-I-Jet range of cardiopulmonary resuscitation drugs: a unique 2.5% thiopentone sodium dispensing kit in both 2.5 g and 5.0 g presentation; Laryng-O-Jet laryngo-tracheal anaesthesia device and a recently introduced disposable endotracheal/endobronchial drug delivery cannula—Trach-O-Jet.

INTERSURGICAL

Crane House, Molly Millars Lane,
Wokingham, Berkshire RG11 2RZ
Tel. 0734-795579; Fax 0734-795555
Sales Director: Stephen Williams

Intersurgical is the British manufacturer of a wide range of disposable products for anaesthesia and respiratory care. The range of anaesthetic breathing systems incorporates the unique disposable Intersurgical APL valve, offering the anaesthetist a lightweight option and eliminates the possibility of cross infection.

Systems in the range include all the most popular Mapleson configurations: Mapleson A—Magill and Lack, Mapleson C—resuscitation, Mapleson D—Bain, and Mapleson F—Ayres T-Piece.

The range of Intersurgical breathing filters are ideal for use in anaesthesia. The Filta-Therm HMEF has been designed for positioning at the patient, offering both bacterial/viral protection combined with heat and moisture exchange. The Filta-Guard is a bacterial/viral filter only for positioning at the equipment connection—both products offer 99.999% filtration efficiency ensuring protection of the patient, equipment and working environment. Other products in the range include 8.5, 15 and 22 mm breathing systems, catheter mounts and products for oxygen therapy.

IVAC

Intec 2 Building, Wade Road,
Basingstoke, Hampshire RG24 0NE
Tel. 0256-474455; Fax 0256-463770
General Manager (M.D.D.): Steve Thornton

IVAC is a supplier of a range of infusion devices including volumetric instruments, syringe pumps and PCA pumps. The IVAC 560/565 volumetric pumps have the ability to measure all in-line pressures and offer maximum safety for infusion of critical drugs requiring fast time to alarm, and warning of occlusion and/or possible infiltration risks. IVAC also supplies the highly accurate IVAC 590 and 597 volumetric pumps.

IVAC also supplies a range of highly accurate syringe pumps including the IVAC P4000 for i.v. anaesthesia. The IVAC 770 variable pressure syringe pump facilities include integral dose rate calculations and variable pressure alarm settings.

To complete the product range, IVAC supplies electronic infrared thermometers.

JADE MEDICAL LTD

Sentinel House, Recreation Road,
Tilehurst, Reading RG3 4UA
Tel. 0734-451881; Fax 0734-451409
Managing Director: John H. Gray

Jade Medical is the U.K. distributor of the "SiteRite" dedicated ultrasound scanner for central venous access. This miniature, battery-powered device enables cannulation of the internal jugular vein (and other frequently cannulated vessels) under direct visualization by two-dimensional ultrasound. A needle guide is incorporated into the scanner head which (for internal jugular vein cannulation) is placed over the sternocleidomastoid muscle. The vessels beneath are readily identified and differentiated, and the needle guide is centred over the internal jugular vein. A standard 17- or 18-gauge needle is advanced with constant aspiration down the guide and may be seen to deform the anterior aspect of the vein. As the needle punctures the vessel, the wall is seen to spring back and simultaneously blood is obtained in the syringe. The technique may be learned quickly and significantly reduces access time, number of attempts and complications whilst improving patient comfort and safety.

JANSSEN PHARMACEUTICAL LTD

Grove, Wantage, Oxon OX12 0DQ
Tel. 0235-772966; Fax 0235-772121
Product Manager: Terri Cooper

Janssen Pharmaceutical Ltd is a long established research-based company responsible for the development and manufacture of a range of products for use by the anaesthetist.

Many U.K. anaesthetists routinely give an i.v. analgesic to provide pain relief during and after operation. This practice gained in popularity with the introduction of new i.v. analgesics from Janssen which provided greater cardiovascular stability than earlier agents such as morphine. These compounds have helped open the way to new anaesthetic techniques making possible heart transplant operations and major brain surgery. The first individual ever to receive an artificial heart was anaesthetized with a product of Janssen research.

The Janssen Anaesthetists Information Service provides news of forthcoming symposia, and through *Ad Referendum* details of recent publications in anaesthesia are circulated to over 2000 anaesthetists in the U.K. *Ad Referendum* is also available to doctors and researchers in the field of anaesthesia in countries outside the U.K.

JMW MEDICAL & JMW SYSTEMS

Systems House, Pentland Industrial Estate, Loanhead,
Midlothian EH20 9QH
Tel. 031-440 3633; Fax 031-440 3637

JMW supplies the full range of patient and fluid warming systems. The Thermomat patient warming system is available in a range of mattress sizes from neonatal to full recovery bed. The control units vary from simple bed warming to multiple output battery powered transportable units.

The Thermofluid range of products are designed to provide low cost, high efficiency blood or fluid warming. The units are robustly constructed for long life.

JOHNSON & JOHNSON MEDICAL LTD

Coronation Road, Ascot,
Berkshire SL5 9EY
Tel. 0344-782626; Fax 0344-872599
Product Manager: Mrs S. A. Perrin

Cidex Activated Glutaraldehyde Solution represents a solution to the problem of effective disinfection of anaesthetic equipment because of its unique combination of instrument safety, spectrum of activity and speed of action. Cidex Solution has been used with confidence for the sterilization and disinfection of heat labile and delicate medical and surgical equipment including rigid and fibreoptic endoscopes, anaesthetic face masks, endotracheal tubes, rebreathing bags, breathing tubes and airways etc. Cidex Long Life Activated Glutaraldehyde Solution offers the same range of cidal activity as the original 14 day product and additionally incorporates a fresh mint odour and wetting agents which allow the solution to penetrate even the most intricate parts. Cidex solution disinfects, killing all vegetative micro-organisms and viruses including hepatitis B in 10 min, TB in 1 h and sterilizes, killing all forms of microbial life, including spores, in 10 h.

Other inherent benefits offered by Cidex Solution include a high degree of resistance to inactivation by organic soilage, compatibility with common surgical materials, including carbon, steel, rubber, copper, brass, chrome plate and aluminium, and simplicity in use with visual evidence of activation.

KABI PHARMACIA LTD

Davy Avenue, Knowhill
Buckinghamshire MK5 8PH
Tel. 0908-661101; Fax 0908-603950
Product Manager: Steve Whitney
(Hospital Products Division)

Kabi Pharmacia supplies both Deltec ambulatory drug delivery systems and IMED volumetric infusion pumps. A complete range of i.v. management systems that caters for both the hospital and alternative site care market, is also available.

The IMED range of volumetric pumps, in particular the Gemini instruments offer two-in-one systems that can operate as either pump or controller, with secondary mode capability in either micro or macro infusion control in one device. The two-channel Gemini PC2 gives two independent channels with the same flexibility as the single Gemini PC1, and both offer fast detection of occlusion at low-flow rates, air in line detection and full compatability through an RS232 interface to all computer systems.

The Deltec range of systems include: the Port-a-Cath implantable access systems with the revolutionary port Passport for arm replacement, the Cadd range of ambulatory i.v. pumps, especially designed for TPN, PCA and oncological and antibiotic therapy, where pre-programmed, continuous, intermittent or patient controlled drug administration is needed.

KENDATA PERIPHERALS LTD

Nutsey Lane, Totton,
Southampton SO4 3NB
Tel. 0703-869922; Fax 0703-860800
General Manager: John Holder

Kendata supplies optical mark readers (OMRs) which, together with associated software, are used widely for data capture for audit purposes, notably in anaesthetics. These may be used as stand alone systems linked to a single desktop computer or as part of a larger theatre management system. Closely allied to the success of the readers in capturing data is the custom design-and-print service for the associated documents. Tailored to the needs of each user, these documents are used to collect the data "at the sharp end" by the use of single pencil or pen strokes. The need for transcription of data by others is eliminated. Data is entered directly into the computer memory without the use of a keyboard in a fraction of the time taken to do it manually. The use of paper as the data-collecting medium keeps revenue costs to a minimum and ensures that the system is flexible enough to cope with changing requirements. An installed system is not limited to its original function, but can be used for a wide variety of other activities requiring data capture. Kendata offers full support with document design and evaluation of new applications.

KEYMED

KeyMed House, Stock Road,
Southend-on-Sea, Essex SS2 5QH
Tel. 0702-616333; Fax 0702-465677
Medical Sales Manager: P. R. R. Goodman

A simple, safe and accurate method of helping with the difficult intubation is now available from KeyMed in the form of two fully immersible fibreoptic intubating laryngoscopes.

The Olympus LF-2 is designed specifically for anaesthetists and can be introduced either transnasally or transorally on the awake or fully anaesthetized patient, with minimal patient discomfort and trauma. The Olympus LF-P is a specialized, flexible intubating laryngoscope designed for safe tracheal tube placement in paediatric and neonatal patients.

For therapeutic applications, especially in the ITU, the new Olympus BF-XT20D flexible bronchoscope, with a 3.2 mm channel, is particularly useful for aspiration of fluids and secretions in patients on long term ventilation or for aspiration of blood.

For flexible nasopharyngoscopy, KeyMed has the specially developed Olympus ENF range of nasopharyngoscopes.

A number of KeyMed teaching video tapes have been produced on the use of the LF-2 intubating laryngoscope and nasopharyngoscope—all are available for purchase or free of charge (short term) loan.

KIMAL SCIENTIFIC PRODUCTS LTD

Arundel Road, Uxbridge,
Middlesex UB8 2SA
Tel. 0895-270951; Fax 0895-274035

Kimal Scientific Products Ltd is a wholly independent British company specializing in the sale and distribution of a range of medical devices and instrumentation.

Kimal is the exclusive U.K. distributor for Arrow International Inc, the pioneers of multilumen central venous catheters. The range includes specialist procedure packs for central venous, peripheral, and arterial catheterization and regional anaesthesia procedures. Kimal also offers a complimentary range of balloon flotation catheters for thermodilution and Swan-Ganz procedures.

KONTRON INSTRUMENTS LTD

Blackmoor Lane, Croxley Centre,
Watford, Hertfordshire WD1 8XQ
Tel. 0923-245991; Fax. 0923-220666
Sales Manager: Howard Pyrah

Kontron Instruments is a British and European manufacturer of advanced medical and scientific instrumentation for diagnostics, monitoring, therapy and data management in the health care field.

Kontron Instruments offers a range of products to monitor and record patient status, from basic ECG and non-invasive BP, through compact configured systems, to comprehensive modular systems with full optical fibre networking. Kontron's intra-aortic balloon pumps are designed for both hospital and transport use; defibrillators are ideal for both emergency defibrillation and elective cardioversion, whilst Kontron offers ventilators for use in theatre and ICU, and situations where piped gases are not available. A new range of infusion devices includes simple syringe drivers through volumetric pumps to patient controlled analgesia and i.v. anaesthesia delivery systems.

Kontron's Unit Data and Information System (KUDAIS) provides the basis for an integrated approach to care management. The company's ultrasound technology meets the latest needs in cardiology, internal medicine, obstetrics and gynaecology and neurology in newborn babies, children and adults, and includes Annular array ultrasound, mechanical sector, combined linear and sector systems, echocardiography and flow mapping systems, 2D, Doppler and colour imaging. The diagnostic product range also includes ECG analysis equipment and stat analysers for sodium, potassium, calcium, glucose and haemotocrit.

LAERDAL

Laerdal House, Goodmead Road,
Orpington, Kent BR6 0XH
Tel. 0689-876634; Fax 0689-873800
Managing Director: K. G. Morallee

Laerdal is the world's leading manufacturer of resuscitation training aids and emergency equipment including: standard training aids—Resusci Anne, Resusci Junior and Resusci Baby, for teaching basic life support; advanced training aids—Arrhythmia Anne, for teaching basic life support, arrhythmia recognition and defibrillation; ALS trainer; airway management and infusion trainers; suction equipment—the Laerdal suction unit is the most widely used self-powered portable aspirator noted for its versatility, efficiency and reliability; resuscitators—the Laerdal silicone resuscitators and masks are recognized for their superior efficiency and safety. Made of resilient silicone and transparent polysulfone, they are uniquely easy to clean and sterilize, withstanding hundreds of cleaning cycles at 136 °C; defibrillator—Heartstart 3000 QR, a new semi-automatic defibrillator with monitoring capabilities and strip chart recorder.

LECTROMED U.K. LTD

Unit 23, The Business Centre,
Avenue One,
Letchworth Garden City,
Hertfordshire SG6 2HB
Tel. 0462-481828; Fax 0462-481647
Managing Director: P. R. Crossley

The cerebral function monitor (CFM) originally manufactured by Devices and in use throughout the world is now available in a new Lectromed 5331/5330 form. The modular instrument retains the original format but it is now possible to plug in different amplifiers in the second channel or use the CFM module in a multi-channel recorder so that other parameters such as blood pressure, intercranial pressure, ECG etc, can be recorded alongside cerebral activity.

The Multi-trace range of chart recorders is available from two to eight channels with or without pre-amplifiers allowing either recording from existing monitoring equipment alone, or a complete system including amplifiers and signal conditioning to be supplied.

Isolated amplifiers are available to record a wide variety of parameters.

LEYLAND MEDICAL INTERNATIONAL LTD

P.O. Box 6, Tuer Street, Leyland,
Preston, Lancashire PR5 1XR
Tel. 0772-431151; Fax 0772-456831

For over 100 years Leyland Medical International Ltd has been recognized as a specialist manufacturer of rubber, latex and plastic products. The company produces a comprehensive range of anaesthesia accessories to high standards which include endotracheal tubes, plain and cuffed, endobronchial tubes, oxford tubes, airways, rebreathing bags, corrugated tubes, catheter mounts, oxygen tubing and facemasks.

A recent addition to Leyland's products is a complete range of laser proof metal tracheal tubes for use in laser surgery and includes a baby size designed for 12 to 24 month-old babies.

LIFECARE HOSPITAL SUPPLIES LTD

Scotland Road, Market Harborough,
Leicestershire LE16 8AX
Tel. 0858-431455; Fax 0858-431799
Sales Manager/MD: J. R. Cresswell

Lifecare Hospital Supplies Ltd, a British owned company, specializes in the design and manufacture of inhalation therapy products. The existing range of products consist of the following; Micro-Neb—a small particle high output nebulizer for the administration of drugs. It is available in kit form and is supplied with either a mask or mouthpiece for adult and paediatric use; Tru-Flow Venturi Mask—available with plug-in venturies of various concentrations for adult and paediatric use; Duo-Mask—a dual purpose oxygen and aerosol mask for adult and paediatric use; Easy-Flow Nasal Cannula—a soft vinyl nasal cannula of over the ear design and fitted with anticrush tubing; Secur-i-tube—universal tubing fitted with secure PVC connectors and compatible with a wide range of respiratory accessories; Flex-i-tube—general purpose 22 mm polyethylene tube; Dispenser packed in 50 m rolls for aerosol therapy, ventilator circuits and the extraction of anaesthetic gases from theatres; VenticirKit—custom designed ventilator circuit. A new approach has been taken in the design and application of various mask products resulting in a modular adult and paediatric mask system, with all components totally interchangeable offering complete flexibility.

LIFE SUPPORT ENGINEERING LTD

Robell Way, Storrington,
West Sussex RH20 3DN

Tel. 0903-742322; Fax 0903-745923
Sales Manager: Stuart McOnie

Life Support Engineering designs and manufactures a portable manual resuscitator, a range of oxygen therapy units and peacemaker, a portable analgesic unit.

The manual resuscitator combines oxygen therapy with a resuscitation bag and accessories enabling oxygen enriched resuscitation to be performed at the scene of an accident. The oxygen therapy units are available with a variety of preset fixed flows or variable flow selectors depending on the requirement.

Peacemaker is a portable analgesic unit that administers a pre-mixed gas of 50% oxygen and 50% nitrous oxide (Entonox) to the patient on demand. The high performance sensitive demand valve releases the gas with the slightest inhalation; this ensures that the patient receives pain relief as quickly and efficiently as possible.

LIFEWISE

P.O. Box 170, Kegworth,
Derby DE7 2YF
Tel. 0509 674124
Director: Barbara Schindler

Lifewise was established in 1990 to provide a top quality rental service for transcutaneous nerve stimulators (TENS) for use in childbirth. In addition to the Maternity TENS, Lifewise now supplies a range of TENS for the relief of other pain syndromes. These can be provided on a trial basis to assess suitability for the patient.

LINTON INSTRUMENTATION

No. 1 Forge Business Centre,
Upper Rose Lane, Palgrave, Diss,
Norfolk IP22 1AP
Tel. 0379-651344; Fax 0379-650970
Managing Director: P. Gunning

Linton Instrumentation supplies a range of electromedical equipment including: Neurostim LA nerve stimulator for regional anaesthesia; special insulated needles for precise nerve tracing using currents below 1 mA; Neurostim T4 nerve stimulator for checking the depth of anaesthesia; Transonic Transit-Time ultrasound blood flowmeter for volumetric flow measurements during surgery or extracorporeal procedures.

LRC PRODUCTS LTD

Regent International Division,
North Circular Road, London E4 8QA
Tel. 081-527 2377; Fax 081-503 2094
Marketing Manager: Howard Broadbridge

LRC Products supplies surgical and procedure gloves.

LUXFER U.K. LTD

Colwick, Nottingham NG4 2BH
Tel. 0602-615145; Fax 0602-613890
Sales and Marketing Director: Edward H. Tipton

Luxfer U.K. Ltd is the European division of Luxfer Gas Cylinders, the world's largest manufacturer of seamless aluminium alloy high pressure gas cylinders. Two plants serve a diverse range of markets, from medical and breathing apparatus to fire extinguishers with worldwide support from Luxfer U.S.A. and CIG Australia.

Luxfer U.K. Ltd, Nottingham, produces conventional aluminium alloy cylinders with a water capacity between 1 and 50 litres, in addition to ultralightweight fibre-glass reinforced composite cylinders with portable applications such as breathing apparatus, emergency/rescue equipment, life support, domiciliary oxygen and blood-gas sampling.

Luxfer Small Cylinders, Aldridge, was formed in 1989 to develop new markets for small aluminium alloy gas cylinders. Applications include cylinders for medical gases, Entonox, Boyle's machines, resuscitators, oxygen therapy, safety equipment, laboratory instrument calibration, emergency/life support and in situations which demand stable high purity gases in an extremely easy-to-handle, portable/disposable unit.

MACMILLAN PRESS LTD

Houndmills, Basingstoke,
Hampshire RG21 2XS
Tel. 0256-29242; Fax 0256-810526
Promotion Manager: Rosie Bowies Lyon

Macmillan Press publishes journals and books in both established and new areas of medicine and science.

The journals published include: *Applied and Theoretical Electrophoresis*, *Bone Marrow Transplantation*, *British Journal of Cancer*, *British Journal of Pharmacology*, *European Journal of Clinical Nutrition*, *Human and Experimental Toxicology*, *International Journal of Obesity*, *Journal of Human Hypertension*, *Journal of Dermatological Treatment*, *Oncogene*, *Postgraduate Medical Journal*, *Public Health*, *Molecular Neuropharmacology*, *Leukemia*, *Lupus*, *Paraplegia* and *International Journal of Food Science and Nutrition*.

Most of the titles listed above regularly publish sponsored supplements dealing with proceedings of clinical symposia.

MALLINCKRODT MEDICAL (U.K.) LTD

11 North Portway Close,
Round Spinney,
Northampton NN3 4RQ
Tel. 0604-646132; Fax 0604-646884
Product Manager: Miss J. Balchin

Mallinckrodt Medical (U.K.) Ltd is well recognized for is innovative approach to the disposable endotracheal tube market as well as the patient monitoring market with its range of disposable temperature sensors and probes and invasive pressure monitoring kits.

Mallinckrodt's airway products include the unique Laserflex tube for safe laser surgery with a carbon dioxide laser in the mouth and trachea. This will be available in seven sizes, including three paediatric uncuffed sizes. The innovative Brandt rediffusion system which regulates cuff pressures when nitrous oxide is used in anaesthesia is now available on the RAE and reinforced tubes as well as on a basic tube.

The new Unitrans disposable transducer is available on standard or custom-made kits. It has the added safety feature of a back-calibration port which can be used with the Veri-Cal tester for safe, accurate calibration. Domed kits are also available as standard or custom kits.

The Mallinckrodt Mon-a-Therm family of disposable temperature monitoring probes and sensors gives the customer a vast choice of probes and sensors compatible with Thermistor 400, 700 or thermocouple electronics. Monitors, interface cables and thermocouple adaptors are also available.

MARION MERRELL DOW LTD

Lakeside House, Stockley Park,
Uxbridge, Middlesex UB11 1BE
Tel. 081-848 3456
Senior Product Manager: Martin Ellis

Marion Merrell Dow launched two products with potential use within the intensive care/operating theatre setting. They are: Perfan i.v. (enoximone), an inotrope with vasodilator properties for use in the treatment of acute heart failure. Perfan i.v. has demonstrated efficacy in a variety of clinical settings including weaning from extracorporeal circulation, post-cardiac surgery, and before operation as a pharmacological bridge to transplantation. Perfan i.v. offers improved cardiac performance with little or no change in myocardial oxygen consumption.

Targocid i.m./i.v. (teicoplanin) is a once-a-day glycopeptide antibiotic indicated for the treatment of potentially serious gram-positive infections including those which cannot be treated by other antibiotics e.g. penicillins and cephalosporins. Virtually all gram-positive bacteria are sensitive to Targocid including those resistant to other antibiotics. Targocid has proved highly effective in a wide range of gram-positive infections and to be as well tolerated as penicillins or cephalosporins with superior tolerance to vancomycin.

MARQUETTE ELECTRONICS (G.B.) LTD

Unit 7, Priestley Road, Worsley,
Manchester M28 5NJ
Tel. 061-794 8114; Fax 061-794 6295
U.K. General Manager: Ian A. Eddy

Marquette manufactures an extensive line of defibrillators for hospital and emergency care services all over the world. Models include a portable, and an operating room defibrillator, a semi-automatic system for first responders, a combination defibrillator and 12SL ECG analysis for use with thrombolytic drug therapy. MAC-LAB is a computerized cardiac catheterization monitoring system for haemodynamic ECG and cardiovascular procedures. The TRAM portable monitor with battery back-up memory provides continuous monitoring, and protection of the patient during transport throughout the hospital. The TRAM module also functions as an integral part of the ICU/CCU or theatre monitoring system, resulting in uninterrupted trending of all vital parameters. The new Marquette infrared series of gas analysis systems introduces affordable on-line monitoring for the ICU and theatre environments. Marquette also offers the Advantage® mass spectrometer for anaesthetic gas monitoring.

As a result of Marquette's 25 years of experience in diagnostic electrocardiography, the company offers a complete range of systems from the portable MAC-PC electrocardiograph to the new CENTRA. The CENTRA heart station combines ambulatory ECG, exercise stress testing, resting ECG with interpretation, vectorcardiography, signal averaged ECG for late potential analysis and pacemaker evaluation.

MEDAID HEALTH PRODUCTS

Church View, Grange Road,
Felmersham, Bedfordshire MK43 7EU
Tel. 0234-781480; Fax 0234-781480
Marketing Director: Paul G. Perry

Medaid is a wholly British owned company. It specializes in the manufacture and marketing of TENS equipment, offering a number of different models. The company also has a wide range of accessories for use with TENS.

In addition, Medaid supplies body composition analysis equipment that gives the percentage fat and lean tissue, target weight, target fat, BMR, water content and the total lean and total fat in pounds.

Medaid supplies nebulizers and blood pressure monitors for use at home or in the surgery, and the company has recently acquired pulse oximetry equipment.

MEDASIL (SURGICAL) LTD

Medasil House, Hunslet Road,
Leeds LS10 1AU
Tel. 0532-433491; Fax 0532-429276

Medasil (Surgical) Ltd manufactures a range of products for use in the operating theatre and associated environments. Items with anaesthetic application include the silicone Biteguard, the Medasil breathing circuit and a range of anaesthetic airways.

The Biteguard is moulded from radio-opaque silicone rubber, and is widely used to provide dental protection during endoscopic examination or anaesthetic intubation.

MEDEX MEDICAL INC

St Crispin Way, Haslingden,
Rossendale, Lancashire BB4 4PW
Tel. 0706-212236/7; Fax 0706-218834

Medex Medical Inc (U.K.) is a wholly-owned subsidiary of Medex Inc (U.S.) which has been established over 30 years and manufactures and markets a comprehensive range of critical care products. Medex Infusion Systems Division manufactures a range of infusion pumps with the latest computer technology, but are easy to programme and even simpler to operate. Syringe pumps operate with any size (1–60 ml) syringe of up to eight specified makes in several modes including a body-weight mode. A range of disposable kits for total i.v. anaesthesia, parenteral nutrition and other procedures complement the syringe pump range.

With Novatrans II reusable pressure transducers, Medex offers the opportunity of contributing to environmental protection by positively and significantly reducing electronic waste. Novatrans II is part of a complete and flexible pressure monitoring system.

MEDIC-AID LTD

Hook Lane, Pagham,
West Sussex PO21 3PP
Tel. 0243-267321; Fax 0243-262556
Hospital Product Manager: Karen Lillington

Medic-Aid Ltd is a wholly British owned Company specializing in the manufacture of oxygen and aerosol delivery systems. These include a high flow CPAP system which eliminates all reservoir bags, water jars and blenders, a low cost ventilator, ideal for transporting with full patient control. Completing the range is a full selection of nebulizers and humidifiers built to 22 mm fitting standards.

MEDICAL-ASSIST LTD

Commerce Way, Colchester,
Essex CO2 8HH
Tel. 0206-792800; Fax 0206-798434
Marketing Manager: James Hibbins

Medical-Assist Ltd is the exclusive supplier of the Wallace range of British made surgical devices to the U.K. The intravascular range includes Wallace cannulae, dialysis equipment, a range of ergonomically designed i.v. hand and foot splints and the Y-Can infusion device.

Medical-Assist Ltd is a member of the Smiths Industries Medical Systems group of companies. See HG Wallace for further details.

MEDICOM LTD

The White House, Lodge Road,
London NW4 4DD
Tel. 081-203 9686; Fax 081-203 9686
Managing Director: Steve Evans

The Hayek oscillator, distributed by Medicom, is an external high frequency oscillator–ventilator, used to assist, augment or replace spontaneous ventilation for healthy and unhealthy lungs. It is designed for use in intensive care units (neonates, babies and adults), in operating theatres for anaesthetized patients and at home. The oscillator consists of a light-weight flexible cuirass which is easy to apply, tubing, a power unit, and a user-friendly control unit with keyboard and operating information display. It has a comprehensive set of alarms, and is independent of compressed gases. An important feature of the Hayek oscillator is that both inspiratory and expiratory phases are active and not reliant on passive recoil. As a result, high performance, versatility and full control can be achieved.

MEDIPLAN-DAR LTD

Mediplan House, Market Place,
Warwick CV34 4SL
Tel. 0926-400096; Fax 0926-493461
Managing Director: J. G. Donovan

Mediplan-Dar Ltd is the U.K. subsidiary of DAR S.p.A. Italy which manufactures and markets a full range of breathing systems for ventilation and anaesthesia.

A comprehensive range of 14 sterile packed bacterial/viral filters, combination filter/HMEs and pure HMEs is available, from the Hygroster, for long term, high performance bacterial/viral filtration, to small low cost bacterial filters for patient or machine end use.

Mediplan-Dar also supplies the smooth bore breathing circuits with elastomeric connectors for anaesthesia and ventilation as standard or custom built.

A recent innovation has been the launch of the new Extendible range of circuitry and catheter mounts and a low cost light weight system with a Memory hold feature.

MEDIVISION LTD

16 Isbourne Way, Broadway Road,
Winchcombe,
Gloucestershire GL54 5NS
Tel. 0242-604184; Fax 0242-604191
Director: Jeremy Lord

Medivision supplies colour display systems, central stations and theatre slaves. Mediview is a six-channel universal colour slave that processes waveform and numeric data from most types of patient monitor for display on video monitors with screen sizes from 10 to 27 inches.

Facilities include BP trend, freeze, user programmable memories, and variable sweep speeds. Although designed for theatre use, Mediview can also be used for electrophysiology as sweep speeds up to 100 mm s^{-1} can be displayed.

The Miniview ECG monitor station is a universal six channel ECG display and alarm system for central station applications.

The Maxiview central station is a sophisticated 12-channel ECG and BP system with alarms, pop-up review windows and chart recorder.

MICRO MEDICAL LTD

P.O. Box 6, Rochester,
Kent ME1 2AZ
Tel. 0634-843383; Fax 0634-830814

Micro Medical Ltd is a specialist designer and manufacturer of portable pulmonary function equipment, supplying a worldwide market. Established in 1983, Micro Medical offers an extensive range of spirometers, from the hand held Micro Spirometer measuring FEV_1 and FVC, to computer-based flow/volume systems with database facility.

More recently an electronic data storage spirometer for clinical trials and a portable airways resistance meter have been added to the range.

MSA (BRITAIN) LTD

East Shawhead,
Coatbridge ML5 4TD, Scotland
Tel. 0236-24966; Fax 0236-40881
Medical Marketing Executive: John Harris

MSA (Britain) Ltd provides a full sales facility including service support in the U.K. for the medical products manufactured by its associate company Catalyst Research, in the U.S.A. The Mini OX I, II and III oxygen monitors are suitable for in-line use on any anaesthetic machine or ventilator. The Mini OX V is a portable pulse oximeter. It is lightweight, compact and has a long battery life. With its high sensitivity and advanced motion artefact rejection, the Mini OX V is suitable for use in all areas of transport even when poor perfusion is a problem.

The Mini CAP 100 is a stand-alone fully featured capnograph, with automatic calibration and advanced fluid handling for use in theatre, ICU and A&E.

The unique Mini CAP III completes the range. This is a portable qualitative carbon dioxide device. It rapidly and accurately verifies correct intubation even after cardiac arrest. After intubation it monitors continuously for extubation or apnoea and it is also extremely useful as a disconnect alarm on a portable ventilator.

MSB LTD

Ramsbury, Marlborough,
Wiltshire SN8 2RB
Tel. 0672-20055; Fax 0672-20044
Director: Cliff Andrews

MSB is an independent British company specializing in solid state disposable ECG electrodes for the Health Care industry. The range of products include: Biotabs, a diagnostic ECG electrode system which is a safe, cost effective alternative to reusable suction electrodes; Unilect universal ECG electrodes, suitable for all monitoring procedures including stress testing. They are gel free, solvent-free, skin-compatible and cost effective with no wastage; Monitab which has all the benefits of standard Unilect with an off-set-tab; Biotrace-N neonatal pre-attached lead wire ECG electrodes which are durable bio-adhesive, skin friendly and available with 4 mm socket or DIN standard fittings; Solo Defib defibrillation electrodes have been designed for use with the latest advisory defibrillation equipment; Solo Defib Pads are used with conventional paddles and adhere to the skin and protect the patient from burns.

NEOTRONICS MEDICAL LTD

Parsonage Road, Takeley,
Bishop's Stortford,
Hertfordshire CM22 6PU
Tel. 0279-870182; Fax 0279-870377
Sales Director: Stan Cherry

Neotronics Medical is one of the operating divisions of Neotronics Technology Plc. Neotronics Medical manufactures and markets a range of pneumatic resuscitation equipment, pneumatic and electropneumatic ventilation equipment and basic monitoring. The ERA Resuscitator is designed to resuscitate small children (250 ml–1.2 litre) to large adults. It has a fixed I:E ratio of 1 to 2 throughout its entire range, a manual trigger for use in CPR and drive gas consumption is minimal. The unit comes in a complete kit and oxygen therapy and suction are also available. Neotronics Medical also manufactures the Breathco Monitor used in checking carbon monoxide concentrations in breath for smoke inhalation victims, anti-smoking clinics, etc.

The other operating divisions of Neotronics Technology plc manufacture air flow and velocity measuring equipment as well as portable and fixed gas detection systems.

NEUROSCIENCE LTD

Essex Court, Ashton Road,
Harold Hill, Essex RM3 8UD
Tel. 04023-81900; Fax 04023-81886
Sales Manager: Francis Norris

Neuroscience Ltd is a British company which manufactures multi-channel EEG and evoked potential monitoring systems designed for use in intensive care and the operating theatre.

NH EASTWOOD & SONS LTD

118 East Barnet Road, Barnet,
Hertfordshire EN4 8RE
Tel. 081-441 9641; Fax 081-441 2540
Director: P. R. Eastwood

NH Eastwood supplies Mini-TENS modulated transcutaneous electrical nerve stimulators for the chronic relief of pain. The modulated system provides all the basic functions of stimulation including continuous and burst, together with the facility of modulating the output.

NICHOLAS LABORATORIES, ROCHE PRODUCTS LTD

225 Bath Road, Slough,
Berkshire SL2 4AU
Tel. 0753-23971 (ext. 2233);
Fax 0753-70340
Group Product Manager: N. G. Rabouhans

Nicholas Laboratories supplies a number of pharmaceutical products such as, Genticin (gentamicin), Polycrol (aluminium hydroxide-magnesium carbonate), Neo-Mercazole (carbimazole), Electrolade (oral rehydration salts). The company also supplies a micro-opaque range of barium sulphate-based contrast media.

NIKOMED LTD

Trinder House, Free Street,
Bishop's Waltham,
Hampshire SO3 1EE
Tel. 0489-894422; Fax 0489-893322
Operations Manager: Mike Coleman

Nikomed Ltd is a major supplier of single use products for anaesthetics, including ECG monitoring and diagnostic electrodes, diathermy return electrodes for all generator makes, and a range of i.v. dressings for both peripheral and central lines, providing security and prevention of infection.

Also available is a comprehensive range of atraumatic needles for use in spinal anaesthesia. Sizes from 22–27-gauge are available, with or without integral introducer. The polymedic needle features a conical elliptic tip, with no cutting edges, resulting in minimal tissue damage; a large lateral eye near to the distal tip, allows the anaesthetic to be delivered accurately.

New product introductions include a manual resuscitation system available in three sizes—adult, paediatric and neonatal. The bags and masks are made of silicone and may be re-used. A range of defibrillators manufactured from hydrogel are available at competitive prices.

OAKFIELD INSTRUMENTS LTD

Oakfield Industrial Estate,
Stanton Harcourt Road, Eynsham,
Oxon OX8 1JA
Tel. 0865-882532; Fax 0865-883970
Sales Manager: John Giddings

Oakfield Instruments is a British Company specializing in the provision of nuclear medical and electronic equipment.

Cardioscint, left ventricle function monitor utilizes standard techneteum red blood cell labelling techniques to provide single probe ventriculography. Real time beat-to-beat and ECG-gated ejection fractions are displayed. Cardioscint provides both short and long term left ventricle function monitoring and is particularly useful in monitoring rapid, transient changes.

Mediscint dynamic organ function monitor supports up to four probes and can be used with either single or dual isotope techniques. Real time acquisition curves are displayed and a data reduction package is available for time/activity curve processing. It can be used for a wide range of techniques, e.g. cerebral blood flow, muscle blood flow, renography, gastric emptying and lung permeability. Zinetics Accusite pH provides a rapid and accurate method of positioning enteral feeding tubes and checking position during use. The Graphprobe "on demand" gastric pH monitoring system is more accurate, safer and more convenient than litmus testing.

OHMEDA

Ohmeda House,
71 Great North Road,
Hatfield, Hertfordshire AL9 5EN
Tel. 0707-263570; Fax 0707-260065
Marketing Director: Bryn Gittins

BOC Healthcare products previously marketed by two divisions (Ohmeda and Viggo-Spectramed) are now marketed under one company, Ohmeda. The Anaesthetic equipment range features the Excel and Modulus Anaesthetic Systems together with a range of integrated and stand-alone ventilators. Respiratory monitoring products include the Biox pulse oximeters and the 5250 respiratory gas monitor.

The Venflon Cannula is the flagship of a comprehensive range of infusion therapy products. Venous catheters include the Hydrocath triple lumen and the unique Cuff-Cath Duo polyurethane tunnellable catheter. Cardiac output measurement products include Pentapace and Criticath thermodilution catheters. A wide range of pressure monitoring units incorporating the DTX are available, supported by an extensive range of accessories.

The company manufactures a full range of suction and oxygen therapy equipment to complete the anaesthetic range.

ORGANON TEKNIKA

Science Park, Milton Road,
Cambridge CB4 4FL
Tel. 0223-423650; Fax 0223-420264
Pharmaceutical Group Product Manager: Alan Stern

Organon Teknika Ltd, one of five companies which make up the Pharma Division of AKZO, is active in the research and development of non-depolarizing neuromuscular blocking drugs. Organon Teknika currently supplies two non-depolarizing muscle relaxants: Pavulon (pancuronium bromide) and Norcuron (vecuronium bromide). Norcuron has been in clinical use in the U.K. since 1983 and is now well known for its rapid onset, predictable duration of action, and easy and early reversal. Norcuron has a wide therapeutic safety margin, minimal cumulation and histamine release, and a low incidence of adverse drug reactions. Reflecting this, the data sheet for Norcuron was amended in 1989 to allow the administration of four times the ED$_{95}$ in a single bolus injection.

Norcuron may be used in short operations, in a standard single bolus dose; for intermediate operations, in a large initial bolus dose or intermittent top-up doses; or for longer operations, by continuous infusions or intermittent top-up doses. Norcuron is available in packs of 20 vials, each containing 10 mg of vecuronium bromide in a buffered freeze-dried form, with 20 5 ml ampoules of water for injection as solvent. Organon Teknika also manufactures bleeding time devices. Simplate I and II in both non-retractable and retractable (R) blade formats may be used to assess the risk of prolonged bleeding before surgery in certain at-risk patients.

OXFORD UNIVERSITY PRESS

Walton Street, Oxford OX2 6DP
Tel. 0865-56767; Fax 0865-56646
Managing Director: John Manger

Oxford University Press is an international publishing house established by the University of Oxford. It exists to serve the purposes of the University by furthering the advancement and spread of learning in the humanities, arts, sciences and social sciences through the publication of books and scholarly journals.

The Press publishes an extensive range of books dealing with anaesthesia and related subjects. Titles currently published by the Press include *The Management of Chronic Pain* by A. W. Diamond and S. W. Coniam, *A Handbook of Paediatric Anaesthesia* by Stephen J. Mather and David G. Hughes, *Anaesthesia for Ophthalmic Surgery* by Sobhy Morsy Mostafa, and *The Management of Acute Pain* by Gilbert Park and Barbara Fulton.

PALL BIOMEDICAL LTD

Europa House, Havant Street,
Portsmouth PO1 9PD
Tel. 0705-753545; Fax 0705-851298

The Pall breathing system filter is a cost effective and safe method of providing individually humidified anaesthesia. The hydrophobic Pall filter offers a > 99.9% efficient barrier to the passage of bacteria and viruses. Its versatility enables the filter to act as a mobile barrier, allowing the patient to be safely transferred around the hospital, thus eliminating the need for ventilator and circuit re-sterilization. The Pall Filter connects simply to any breathing system providing optimal humidification and removing the need for conventional and complex heated humidification systems. It has now also been designed with integral carbon dioxide monitoring port and tethered cap.

Pall Biomedical Ltd also manufactures a range of Pall Posidyne 96-h i.v. filters providing patient protection from inadvertent air, microbial and endotoxin contamination.

Pall also have filtration expertise in the field of blood transfusion and cardiac surgery.

PARKE-DAVIS RESEARCH LABORATORIES

Lambert Court, Chestnut Avenue,
Eastleigh, Hampshire SO5 3ZQ
Tel. 0703-620500; Fax 0703-629818

Ketalar (ketamine hydrochloride) is a parenteral general anaesthetic indicated for the following: as a sole anaesthetic agent for diagnostic and surgical procedures. When used by i.v. and i.m. injection, Ketalar is best suited for short procedures. With additional doses or by i.v. infusion, Ketalar can be used for longer procedures; for the induction of anaesthesia prior to the administration of other general anaesthetic agents; to supplement other anaesthetic agents.

Ketalar is available as solutions intended for i.v. or i.m. injection in concentrations containing the equivalent of either 10, 50 or 100 mg ml^{-1} ketamine base. The latter two concentrations contain 1 in 10000 benzethonium chloride, as a preservative. The 10 mg ml^{-1} solution has been made isotonic with sodium chloride.

PENLON LTD

Radley Road, Abingdon,
Oxon OX14 3PH
Tel. 0235-554222; Fax 0235-555252

Penlon manufactures and distributes anaesthetic equipment to suit the national requirements of anaesthetists worldwide. Penlon's comprehensive range of products comprise four anaesthetic machines, paediatric and adult ventilators for anaesthesia and intensive care, a wide choice of PPV Sigma vaporizers, an extensive range of conventional and fibrelight laryngoscopes, draw-over anaesthesia equipment, resuscitation and emergency equipment.

The AM1100 anaesthetic machine, incorporates a paramagnetic oxygen analyser and control system, with an AHD. Additionally, the AM1100 allows the choice of a suitable patient monitoring system to be "built" into the top pod or to be placed on a conventional monitor shelf.

The AM700 anaesthetic machine has been designed to provide optimum flexibility to suit individual needs. The comprehensive range of optional features and accessories include a built-in paramagnetic oxygen analyser with AHD.

PENNCO MEDICAL SERVICES

7 Heathgate, Agincourt Road,
London NW3 2NT
Tel. 071-284 2824; Fax 071-284 2675

Pennco Medical supplies electromedical and anaesthetic equipment including: Seabrook hyper-hypothermic systems for microprocessor controlled patient warming or cooling; First Temp Genius Tympanic Membrane Thermometer for providing accurate non-invasive core temperature readings within 2 s; vascular access products, including dual and single lumen catheters and arteriovenous shunts; Wallach Cryosystem pain blockers incorporating an ultra sensitive nerve stimulator to facilitate precise location of the freezing tip.

PFIZER LTD

Ramsgate Road, Sandwich,
Kent CT13 9NJ
Tel. 0304-616161; Fax 0304-616221
Sales Services Manager: D. J. Halfacre

Pfizer Ltd supplies a wide range of pharmaceutical preparations including antibiotics.

PHARMACIA DELTEC

Davy Avenue, Knowlhill,
Milton Keynes MK5 8PH
Tel. 0908-603877; Fax 0908-690091
Divisional Manager: Cathy Stokes

Pharmacia Deltec is one of the operating divisions of Pharmacia Biosystems Ltd. Deltec supplies ambulatory infusion pumps and implantable drug delivery systems for extradural and intraspinal use, i.v., arterial and peritoneal access. The Cadd PCA infusion pump is intended for chronic and palliative pain relief as well as for use in the postoperative environment where it can be used with a pole mount. The Cadd PCA 5800 delivers continuous infusions only, patient activated bolus doses only, a combination of both or a clinician activated bolus. It can be programmed in mg/ml or ml/h, (0 to 99.5 mg/h or 0 to 20 ml/h as a continuous rate with a bolus of 0 to 99 mg or 0 to 6 ml). The 5800 will record the number of bolus doses given, as well as the number of attempted boluses by the patient.

Other pumps in the range include the Cadd I for continuous infusion and the Cadd plus for intermittent infusion of antibiotics.

PHYSIO-CONTROL UK

Intec 2, Units 10–20, Wade Road,
Basingstoke, Hampshire RG24 0NE
Tel. 0256-474455; Fax 0256-463770
Country Manager: Trevor J. Sams

Physio-Control, a world leader in acute cardiac care systems, has revolutionized the present concept of defibrillators. The Lifepak 9P defibrillator/monitor with external pacing, unique documentation system, optional shock advisory module and hands off defibrillation, together with the Lifepak 10 defibrillation/monitor/pacemaker offering not only the portability and versatility of its contemporaries, but also an optional built-in external pacing system, together with the new concept in code summary analysis, are all unique to Physio-Control. In addition, the Lifepak 300 automatic advisory defibrillator has a patented motion artefact detector system and an integrated paper recorder.

PLATON INSTRUMENTATION LTD

Platon Park, Viables, Basingstoke,
Hampshire RG22 4BS
Tel. 0256-470456; Fax 0256-63345

Platon Instrumentation supplies a wide range of flow and pressure measurement and control equipment for anaesthesia.

The Gapmeter variable area flowmeter has found universal favour for measuring flow rates of anaesthetic gases. It is reliable and accurate, comprising two components indicating float and borosilicate tube, which operate without friction being both stable and sterile, and able to function indefinitely without deterioration and therefore retaining the greatest possible precision of measurement.

The Platon Flow Laboratory tests and certificates flowmeters of any type or manufacture specified in the British Calibration Service catalogue. The modern temperature controlled laboratory is well equipped for volume, pressure, temperature and time measurements, all certified to National Physical Laboratory standards.

PNEUPAC LTD

Crescent Road, Luton,
Bedfordshire LU2 0AH
Tel. 0582-453303; Fax 0582-453103
Sales and Marketing Director: P. I. Webb

PneuPAC Ltd is a multi-divisional medical company with ventilator and anaesthetic equipment manufacturing divisions.

The Ventilator Division manufactures a comprehensive range of portable, gas powered ventilators. Ventipac 5 is an anaesthetic ventilator suitable for driving any open circuit (e.g. Bain, Mapleson A & D, Lack or with slight modification, the pneuPAC circle system). The unit is independent of hospital electrical systems. TransPAC is intended for use as a portable ventilator for inter- and intra-hospital transport which with its built-in controlled mandatory ventilation facility, responds with the sophistication of much larger hospital ventilators.

The Lamtec Anaesthetic division produces a wide range of anaesthetic machines varying from the large 900 IMS to the hand transportable 110. The IMS has built-in monitoring systems for oxygen, anaesthetic agent and carbon dioxide. It is also capable of providing a hard copy record of the total procedure.

Additionally, the range includes the 605 Anaesthetic Agent Monitor, a stand alone unit with very sensitive and fast reaction time. PneuPAC Lamtec also produces a non-magnetic machine for MRIS Scanning Departments.

PORTEX LTD

Hythe, Kent CT21 6JL
Tel. 0303-260551; Fax 0303-266761
Director: R. M. Drury

Portex manufactures a range of single use plastic medical devices used mainly in anaesthesia, respiratory care and thoracic surgery. Blue Line tracheal tubes and related connector systems for adult and paediatric use are complemented by a wide range of specialist products designed for longer term critical care. Portex tracheostomy tubes and Steri-cath closed suction systems provide an ideal combination of patient comfort and safety features for both patients and medical staff.

Portex regional anaesthesia products are used worldwide, with Portex extradural catheters and procedure kits being developed continuously to reflect changes in clinical practice.

More recently, heat and moisture exchangers and bacterial/viral filters have joined the expanding range of single use sterile plastic products, while the RSP temperature monitors and their probes, fitted into tracheal tubes and other catheter systems, provide the anaesthetist with additional facilities aimed at improving clinical efficiency and patient safety.

PPG HELLIGE LTD

8 Weller Drive, Hogwood Lane
Industrial Estate, Finchampstead,
Berkshire RG11 4QW
Tel. 0734-733844; Fax 0734-730254
General Manager: Eric Pearce

PPG Hellige Biomedical Division supplies a wide range of products to the Health Care Service. Products include: patient monitoring devices for ITU/CCU and theatres all of which may be networked and monitored centrally. Several task orientated defibrillators are available for trolley or portable use. An extensive range of electrocardiograph (EK range) devices as well as Holter monitoring and catheterization systems are also available.

PURITAN-BENNETT

Unit 1, Heathrow Causeway Estate,
152–176 Great South West Road,
Hounslow, Middlesex TW4 6JS
Tel. 081-577 1870; Fax 081-577 7762
Director: Ian Chapman

Puritan-Bennett is a major manufacturer of medical equipment designed for use in the ICU, operating theatres, pulmonary function laboratories and homecare.

The Puritan-Bennett product range includes the 7200 series ventilator with a range of options that include flow triggers, graphics and pressure controlled ventilation. The 7200e allows lower specification, the 7200spe incorporates PCV to allow ventilation of paediatric patients and the 7200ae can be built to allow any level of specification required. Other ventilators include the 2801 for hospital or homecare ventilation.

Other products include the oxygen concentrators, liquid oxygen, Companion 515 CPAP system and the Adam nasal pillows delivery system which provides a comfortable solution to sleep apnoea.

Puritan-Bennett provides also an extensive range of flow meters, suction regulators, fittings and accessories, reusable and disposable manual resuscitators. Puritan-Bennett also manufactures the PB3300 system which continuously measures and displays pH, $P\text{CO}_2$, $P\text{O}_2$ and temperature via an indwelling sensor.

RADIOMETER LTD

The Manor, Manor Royal, Crawley,
West Sussex RH10 2PY
Tel. 0293-517599; Fax 0293-531597
Managing Director: Peter R. Lovett

A measure of oxygen transport and release to the tissues is provided by the new ABL520 pH/blood-gas analyser which incorporates blood oximetry parameters with conventional blood-gas data. Other ABL models offer traditional blood-gas measurements. A bench oximeter, the OSM3 can be linked to these analysers to provide a comprehensive pH, blood-gases, electrolytes and blood oximetry profile.

Non-invasive monitoring of oxygen and carbon dioxide can be performed with the TCM3 transcutaneous monitor Tina, and OXI is an easy to use pulse oximeter. The QS range of preheparinised syringes can help clinicians avoid the errors commonly found in the pre-analytical stage of blood-gas analysis.

RAYMAR

Unit 1, Fairview Estate, Reading Road,
Henley-on-Thames, Oxon RG9 1HE
Tel. 0491-578446; Fax 0491-410233
Marketing Manager: A. O'Collins

Raymar supplies a range of TENS units. A single channel unit has adjustable pulse frequency and amplitude. Dual channel units have adjustable pulse width (40–200 msec) and frequency (2–120 Hz). Burst and modulation of both width and frequency are features of the most sophisticated units.

Units are supplied normally with carbon rubber electrodes and karaya gel pads. Alternatively, there is a range of reusable electrodes. All units operate using alkaline or rechargeable batteries. A full range of units and accessories are available on request.

RECKITT & COLMAN PRODUCTS

Dansom Lane,
Kingston-Upon-Hull, HU8 7DS
Tel. 0482-26151; Fax 0482-25322
Director of Medical Affairs: N. C. Varey

One of Reckitt & Colman's major interests is in pharmaceutics. Temgesic is a strong analgesic with a potency approximately 40 times that of morphine, for use in moderate to severe pain. It is advailable both as an injection and as a sublingual tablet. It has a wide margin of safety and a substantially lower dependence liability than pure agonist analgesics. Major areas of usage within hospitals include anaesthesia, oncology, ischaemia, dermatology (burns) and rheumatology. Temgesic has a favourable haemodynamic profile which, combined with powerful analgesic properties, has also made it a useful agent in coronary cases.

REGENT HOSPITAL PRODUCTS

LRC Products Ltd
North Circular Road,
London E4 8QA
Tel. 081-527 2377; Fax 081-503 2094
Marketing Manager: Brian Smith

Regent Hospital Products is a division of the London International Group and supplies an extensive range of surgeons' and procedure gloves, including Biogel Surgeons' gloves and featherlite procedure gloves.

Of particular interest to anaesthetists is Biogel Diagnostic, a non-sterile version of the proven Biogel Surgeons' gloves. Biogel Diagnostic is 100% tested, powder-free and available in eight sizes in convenient dispenser boxes of 25 pairs. Biogel M has extra grip for microsurgery, white Bioguard has an antimicrobial layer to reduce the risk of infection in implant surgery.

ROCHE PRODUCTS LTD

P.O. Box 8, Welwyn Garden City,
Hertfordshire AL7 3AY
Tel. 0707-328128; Fax 0707-338297
Medical Information Executive: Fiona Nicholls

Roche produces a range of anaesthetic products. Alloferin (alcuronium chloride) is a medium-acting neuromuscular blocking agent. It is a derivative of toxiferine, a muscle relaxant of the non-depolarizing type. Its speed of onset is sufficiently rapid to allow intubation, and its comparatively short duration of effect, extendable by repeated doses, enables its use in short or more prolonged procedures alike. Alloferin is available as ampoules containing 10 mg alcuronium chloride in 2 ml, in packs of 10.

Anexate (flumazenil), an imidazobenzodiazepine, is a specific competitive inhibitor of substances which act via benzodiazepine receptors. The hypnotic-sedative effects of the agonist are rapidly reversed by Anexate. Anexate is available as ampoules containing 500 µg flumazenil per 5 ml, in packs of 5.

Hypnovel (midazolam) is a potent imidazobenzodiazepine, forming water-soluble salts which are stable and well tolerated by injection. In clinical use the induction of sleep is the main action. At sedative and anaesthetic doses given i.v. its action is rapid in onset and of short duration. Hypnovel is available as ampoules containing 10 mg midazolam in 2 ml or 10 mg midazolam in 5 ml, in packs of 10.

Prostigmin (neostigmine) is a cholinesterase antagonist potentiating naturally occurring acetylcholine and antagonizing non-depolarizing neuromuscular block. Prostigmin is available as tablets containing 15 mg neostigmine bromide in packs of 100 or ampoules containing 0.5 mg or 2.5 mg neostigmine methylsulphate in 1 ml, in packs of 10.

ROCKET OF LONDON LTD

Imperial Way, Watford,
Hertfordshire WD2 4XX
Tel. 0923-239791; Fax 0923-230212
Marketing Director: S. Hastings

Rocket of London supplies a wide range of medical disposables and electromedical equipment.

RUSCH U.K. LTD

P.O. Box 138, Halifax Road,
Cressex Industrial Estate,
High Wycombe,
Buckinghamshire HP12 3NB
Tel. 0494-532761;
Fax 0494-534223/524650
Market Manager: Milena Duvnjak

Rusch U.K. Ltd is a new company formed from Warne Franklin and Willy Rusch AG. The product range includes the Sprotte atraumatic spinal needle, 32-gauge and 28-gauge spinal catheters for continuous spinal anaesthesia, extradural systems, anaesthesia delivery systems and tracheal tubes.

Rusch has recently become the exclusive supplier of Inspiron and Intestech products in the U.K. Products include: breathing filters, disposable anaesthesia breathing circuits, heat moisture exchangers, oxygen and respiratory therapy disposables, and ventilator circuits.

S&W VICKERS LTD

Ruxley Corner, Sidcup,
Kent DA14 5BL
Tel. 081-309 0433; Fax 081-309 0919
Managing Director: Roy Uncles
Marketing Manager: Chris Worrell

S&W Vickers is the U.K.'s leading supplier of high-technology medical equipment. The company was formed in 1989 as a result of combining Simonsen & Weel and Vickers Medical. S&W Vickers supplies a range of cost effective, high technology products including: Athena monitoring system. A powerful, user-friendly monitor with facilities for networking and connection to patient data management (PDM) systems. A range of plug-in modules further extends its versatility.

S&W monitors. A range of portable, configured and modular monitors for all physiological monitoring.

S&W defibrillators and external pacemakers. Portable, tough and easy-to-use range of defibrillators and external pacemakers.

Datex Flexima. Anaesthetic machine which can be bought both with and without integral monitoring.

Datex monitors. Comprehensive range of theatre monitors, with options for oxygen, carbon dioxide, haemodynamics and anaesthetic agents, all fully computer compatible. This includes the new modular AS/3 colour monitor and the popular Cardiocap range of monitors available in five different versions. The Satlite trans (oxygen saturation) and Normocap 200 (end-tidal carbon dioxide) are portable monitors which can be used during transport. They are also ideal for the recovery area.

Fisher & Paykel. Programmable nerve stimulators and a complete range of humidifiers including theatre versions.

The company also sells the complete range of Ventimask products and disposable ECG electrodes for all types of use.

SABRE INTERNATIONAL PRODUCTS LTD

Manor Farm Road, Reading,
Berkshire RG2 0LQ
Tel. 0734-876111 (ext. 284);
Fax 0734-874813
U.K. Sales Manager: Lester Mendham

Sabre International Products Ltd, formerly Gillette Surgical, manufactures and markets a range of premium quality, sterile, single-use medical products including: crystal clear syringes, hypodermic needles, scalpels and blades and preoperative razors.

Since the formation of Sabre International Products Ltd many new products have been added to the range including: Sabre-Spine spinal needles, Sabre-Disc drug filters, Sabre-Wing winged infusion sets, Micro-Point dental needles, Softy Wash body sponges and Sabre procedure packs.

SERVOMEX PLC

Crowborough, Sussex TN6 3DU
Tel. 0892-652181; Fax 0892-662253
Sales Office Manager: B. Coates

Servomex manufactures a wide range of paramagnetic (magneto-dynamic) oxygen analysers for use in operating theatres, ICU and respiratory research.

The 570A is a BASEEFA certified intrinsically safe portable oxygen analyser with digital read out, powered by internal batteries. A mains powered option is offered. Also available is a 0–1 volt signal output equivalent to 0–100% oxygen.

The 571A analyser has a basic accuracy of 0.1% oxygen and a 90% response time of 7.5 s. It provides similar features to the 570A, and in addition offers two level (high-low) alarm facilities.

For higher resolution requirements in research applications the 1100A oxygen analyser offers a wide dynamic range 0–100% oxygen with resolution of 0.01% oxygen independent of setting of analogue output.

The 1400 series oxygen and CO_2 infrared analysers allow various combinations of 19 inch relay rack or bench top mounting configurations. A wide range of oxygen and carbon dioxide transducers are also available on an OEM basis.

SHERWOOD MEDICAL INDUSTRIES LTD

County Oak Way, Crawley,
West Sussex RH11 7YQ
Tel. 0293-534501; Fax 0293-565353
Marketing Manager: M. A. Noller

Sherwood Medical is a subsidiary of American Home Products Corporation, New York, and is a major supplier of health care products throughout the world. These products include laboratory and liquid handling devices, an extensive range of tubes and catheters, dressings, blood collection tubes, dental needles and devices, urological products, i.v. cannulae and syringes, and needles. Some of Sherwood's better known brand names include Monoject, Argyle, Kangaroo and Aero-Flo.

Aeroflo suction catheter has a unique tip that lessens patient discomfort, risk of mucosal damage and subsequent infection. Cuffed and uncuffed Argyle tracheal tubes are medium-volume, low pressure cuffs which minimize the incidence of cuff-related complications.

Respiradyne pulmonary function monitor is a new low cost way to monitor key parameters of pulmonary function. The easy to use compact Triflo II and Voldyne 5000 offer progressive and volumetric spirometry.

The Intramedicut catheter kit is ideal for i.v. infusion including long-term therapy. It features a polyurethane catheter which can be safely and easily inserted through a plastic cannula. A plastic sleeve allows sterile manipulation of the catheter and locking ferrule.

Kangaroo enteral delivery system, the latest in enteral feeding, is designed for accuracy, reliability and patient safety.

SIEMENS PLC

Siemens House, Windmill Road,
Sunbury-on-Thames,
Middlesex TW16 7HS
Tel. 0932-752421; Fax 0932-752496
General Manager Electromedical:
R. Kirby

Siemens is the world's largest manufacturer of medical engineering equipment.

Products of special interest in the area of anaesthesia include: Sirecust patient monitoring equipment—uniquely intelligent with versatile performance. Servo ventilators—time-controlled volume or pressure-assisted for ventilation control or assisted respiration of adults as well as neonates. Individual synchronous lung ventilation. Integrated monitoring equipment (volume/pressure, inspired oxygen concentration) and safety devices. Anaesthesia ventilators—for re-breathing and non-re-breathing systems. Integrated monitoring of breathing pressure, minute volume and oxygen concentration. Servo gas monitors—for measuring and monitoring anaesthesia gas and oxygen concentrations. Carbon dioxide analysers—for continuous measurement of carbon dioxide concentrations in expired gas, for calculating and displaying the end-expiratory carbon dioxide concentration, effective and ineffective tidal volume, carbon dioxide minute production and carbon dioxide tidal production. Computer-aided ventilation—CAV systems memorize, compute and document patient data.

SIMPLA PLASTICS LTD

Cardiff Business Park,
Cardiff CF4 5WF
Tel. 0222-747000; Fax 0222-747001
Sales and Marketing Director: D. S. Baddley

Simpla Plastics is a U.K. based manufacturer with three main areas of activity—urological disposables, ostomy and cytology. The urological product range includes urine collection bags for both hospital and community use. The 2-litre S4 features a universal connection with safe self-sealing sampling port, anti-reflux valve and wide bore outlet tap, suitable for closed system urine drainage.

The Trident leg bag range of body worn bags for the mobile incontinent patient are available to both hospital and community patients; it incorporates a unique Trident non-return valve, soft fabric backing and reliable outlet tap.

A range of all silicone catheters have been added to the product range.

SOLEX

95 Main Street, Broughton Astley,
Leicestershire LE9 6RE
Tel. 0455-283486; Fax 0455-283486
Sales Manager: Kathie Bettle

Solex supplies a range of electromedical equipment including the SI-1000 mini electrical syringe needle destroyer. The needle destroyer eliminates the need for sterilizing or dealing with disposable needles. Needles are placed in a slide track and upon insertion are completely melted by heat generated by platinum heating elements. The extreme high temperature also kills any infectious diseases and bacteria.

SOS PRODUCTS

198 Higher Road, Urmston,
Manchester M31 1BH
Tel. 061-748 4190; Fax 061-746 8349
Sales Director: A. P. Hickox

Speciality Oxygen Service's (SOS) product range comprises mainly emergency oxygen inhalation and therapy equipment and analgesic (Entonox) equipment. The company also does cylinder testing and the general servicing of regulators and gas valving.

SOUTHERN SYRINGE SERVICES LTD

New Universal House,
303 Chase Road,
Southgate, London N14 6JB
Tel. 081-882 1971; 081-886 7757
Export Manager: T. Pidding

Southern Syringe Services is a distributor of diagnostic products and anaesthetic equipment.

SPECIALISED LABORATORY EQUIPMENT LTD

232 Selsdon Road,
South Croydon,
Surrey CR2 6PL
Tel. 081-681 1414; Fax 081-649 8570
Director, Intensive Care Division: John R. Hill

SLE Ltd specializes in two areas of anaesthesia with infant ventilators and neurophysiology products.

The SLE Newborn 2000 is a microprocessor controlled Pneumatic operated flow device, providing patient triggered ventilation—IMV ventilation and CPCP ventilation. Twelve volt operation is possible and all accessories, filters and patient circuits (disposable and reuseable) are supplied.

SLE markets a series of products for use in intraoperative monitoring. These include compressed spectral array (CSA) of EEG signals, evoked potentials of the visual, auditory and somatosensory systems and brain mapping of global brain activity. These systems can be used in a variety of theatre situations e.g. carotid endarterectomy, bypass surgery and correction of scoliosis. In addition, these systems can effectively monitor the depth of anaesthesia, giving the anaesthetist a visual and/or auditory monitor of cerebral function against which to safeguard the patient.

SLE also runs courses for medical physics technicians on servicing, and ventilator courses for medical personnel.

SPRINGER-VERLAG LONDON LTD

Springer House
8 Alexandra Road, Wimbledon,
London SW19 7JZ
Tel. 081-947 5885; Fax 081-947 4651
Marketing Manager: David Anderson

Springer-Verlag London Ltd. is a leading international publisher who, for over 150 years, has been committed to publishing books and journals of the highest standard in the fields of science, technology and medicine. Leading Springer publications include the journal *Intensive Care Medicine* and the textbook *Care of the Critically Ill* and the *Glossary of Anesthesia*. With offices in Heidelberg, Berlin, London, New York, Paris, Hong Kong, Barcelona, and most recently, Budapest, Springer-Verlag services the medical and academic community worldwide.

STERISEAL DIVISION

Thornhill Road, Redditch,
Worcestershire B98 9NL
Tel. 0527-64222; Fax 0527-592111
Senior Product Manager: Ms V. P. Etterley

Steriseal designs and manufactures a variety of sterile needles, including spinals, extradural, lumbar sympathectomy and regional block. A large range of gauges and lengths are available.

SYNCHRO SOFT

Red Lion Cottage, Catforth, Preston,
Lancashire PR4 0HE
Tel. 0772-690546
Proprietor: Ms Denise Chamberlain

Synchro Soft is a software house specializing in the field of portable data capture. This expertise has been applied to the speciality of anaesthesia, and has resulted in the development of a computerized audit system catering for the specific needs of an anaesthetic department.

The system produces a variety of reports each month; administrative reports giving information about who does what where and when; log-books detailing all cases undertaken by each anaesthetist; and individual and departmental reports of deaths and critical events, to be used as the core of a formal audit process.

In addition, the system can be used to generate occasional reports, quickly and easily, relating to any item(s) of specific interest. A number of evolutions of this system are currently under development, including private practise accounts, pain clinics and intensive care.

TERUMO CORPORATION

P.O. Box 119, Tunbridge Wells,
Kent TN2 5TY
Tel. 0892-26331/2/3; Fax 0892-33868
Sales Manager: J. Thompson

Clear Vision single-use syringes spearhead Terumo's entry into the 1990s. This recent introduction was made available at the request of anaesthetists the world over and is the result of highly specialized treatment of polypropylene.

A further innovation from Terumo is the Preza-Pak II arterial blood-gas syringe incorporating a unique hydrophobic filter which allows air to vent as the blood flows into it but seals once the blood reaches the filter.

Other products available also from Terumo include winged infusion needles, i.v. cannulae, spinal needles, extradural sets and dental needles.

THE U.K. INSTITUTE OF HEALTHCARE

C.E.T.S. Training Centre,
6 Sawrey Street,
Millbay, Plymouth, Devon PL1 3LA
Tel. 0752-225516
Contact: P. A. Carroll

The U.K. Institute of Healthcare promotes and sponsors education and understanding of health care, medical care and treatments, as well as scientific research in the U.K. and in many other parts of the world. It is an involved, caring and active member organization working with the World Health Organisation and other recognized agencies to relieve suffering. For example, each year the Institute of Healthcare sponsors a Mobile Eye Clinic and Camp in some distant village of one of the poorer nations of the world. These Mobile Eye Clinics provide treatment and care of many hundreds of people suffering from some of the severest forms of eye infection, loss of vision and blindness.

The U.K. Institute of Healthcare provides a number of services including training schemes for sales and medical representatives, confidential evaluation of new products and services, training of medical engineers and research and travelling scholarship funding to suitable candidates.

UNIMED (U.K.) LTD

Unimed House,
8 Longmead Industrial Estate,
Shaftesbury, Dorset SP7 8EQ
Tel. 0747-54184; Fax 0747-51800

Unimed (U.K.) Ltd manufactures quality disposable products, sterile and non-sterile for respiratory medicine and anaesthesia. The comprehensive range includes masks, drug nebulizers, humidifiers, (refillable or prefill systems), circuits for ITU, theatre use, scavenging systems, coaxil circuits, catheter mounts, etc. Unimed also supplies the Multi-Fit humidification systems allowing prefill safety using standard sterile water pour bottles. This range now includes BSI approved heater, and the new GIN system offering CPAP. The Multi-Fit range offers a free rental of Heater Unit to new users. Please contact customer services for details.

UNO PLAST (U.K.) LTD

Wykeham Industrial Estate,
Moorside Road, Winchester,
Hampshire SO23 7RX
Tel. 0962-841777; Fax 0962-840622
Commercial Services Manager: Jill Wright

Uno Plast is dedicated to the design, manufacture and supply of sterile, clean-packed, single use products in the areas of urology, gastroenterology, paediatrics, surgery, intensive care and anaesthesia.

The current product range consists of 1000 individually designed items including Vacutip the atraumatic vacuum control suction catheter with Mully tip; several other types of suction catheter including the funnel-ended Mully tip; oxygen catheters and cannulae; Guedel airways; and trachea sets for collecting tracheobronchial secretion specimens.

V A HOWE & CO LTD

Beaumont Close, Banbury,
Oxon OX16 7RG
Tel. 0295-252600/252666 (customer support); Fax 0295-268096
Promotions Manager: Claire Wittekind

V. A. Howe & Company is the U.K. distributor for Nova Biomedical blood-gas and electrolyte analysers. The Nova Stat Profile system has built-in upgradeability featuring the most complete range of critical care analytes on a single whole blood stat sample (pH, $P\text{CO}_2$, $P\text{O}_2$, Na, K, Ca, Cl, glucose and haematocrit). Nova has now added lactate and urea measurements.

Other equipment supplied by Howe include electrolyte analysers, Shimadzu spectrophotometers, spectrofluorimeters, densitometers, thermal analysers, Metrohm electrochemical analysers, Hamilton syringes and diluter/dispensers, Sigma centrifuges, Christ freeze dryers, the Howe Gyrovap centrifugal evaporator and the Howe range of electrophoresis power packs and mini gels.

VIAMED

15 Station Road, Cross Hills,
Keighley, West Yorkshire BD20 7DT
Tel. 0535-634542/636757; Fax 0535-635582
Director: J. S. Lamb

Viamed is an independent British company specializing, as a U.K. agent, in the supply of equipment for critical care areas from neonates to adults.

Teledyne Electronics Devices. TED is the world's largest manufacturer of medical oxygen sensors and a leader in the design and supply of oxygen monitors. Recently released is a new T-7 Long Life Micro Fuel Cell for use in both respiratory and anaesthetic areas.

Diatek Inc, supplies clinical digital thermometers and the Lifescan brain activity monitor.

Mennen Medical offers a range of products with high resolution, colour video displays. A combination of configured and modular software controlled monitors which can be easily interfaced to the users existing stand alone equipment such as Sa_{O_2}, non-invasive blood pressure and capnography. The monitors can be used as part of a data management or data gathering system using PC's or mini computers.

Perspex Products include headboxes, heat-shields, cotlids and bronchiolitis chairs.

HME Ltd. A U.K. company formed by experienced bio-medical electronic engineers to introduce low cost, hi-tech, reliable patient monitors for general use throughout hospitals.

Other products include Thermacot overhead low cost baby warmer, Microstim supramaximal nerve stimulator and Anaestim II nerve locator.

VIGGO-SPECTRAMED

Faraday Road, Dorcan, Swindon,
Wiltshire SN3 5HZ
Tel. 0793-430388; Fax 0793-430031
Market Manager: A. J. Percival

Viggo-Spectramed is a leading supplier in the fields of i.v. therapy and invasive monitoring.

For i.v. therapy, the company offers a wide range of peripheral and central venous catheters and cannulae and a range of associated accessories.

For invasive monitoring the company supplies both reusable and disposable pressure transducers along with a comprehensive range of associated products and accessories which permit continuous venous/arterial monitoring. In addition, complementary products such as cardiac output computers are available.

Viggo-Spectramed also has expertise in the specialized area of balloon flotation pulmonary artery catheters for the measurement of right heart pressures and cardiac output.

VITALOGRAPH LTD

Maids Moreton House,
Buckingham MK18 1SW
Tel. 0280-822811; Fax 0280-823302
Marketing Services Manager:
S. Fletcher

Vitalograph is a world leader in spirometry and lung function testing equipment, offering a range of spirometers from the non-automatic R-model to the sophisticated Compact model with 25 ventilatory tests. Vitalograph's peak flow meter is now available on prescription, and is widely used to monitor patients' responses to drugs and therapy.

VYGON (U.K.) LTD

Bridge Road, Circencester,
Gloucestershire GL7 1PT
Tel. 0285-657051; Fax 0285-650293
Business Development Manager: A. S. Costello

Vygon is Europe's largest independent manufacturer of disposable, surgical and medical devices. The product range is extensive and spans most of the requirements of the acute care centres of the hospital.

Within the range there are single, double and triple lumen CVC catheters manufactured under the brand names Leadercath and Multicath. In addition, there is the Lifecath range of Broviac and Hickman type catheters in both single and double lumen variants. There is also a large range of i.v. Lectrocath and Lectrospiral accessory products which are compatible with commonly used drugs and infusions.

New developments include a cardiac catheter sheath introducer. A sheath introducer (Desivalve) is also available for the introduction of Swan Ganz type catheters. This sheath incorporates a locking device for catheter fixation.

Trach Care is the most recent addition to the Vygon range. Trach Care is a closed tracheal suctioning system which permits continued ventilation and simultaneous tracheal suction without the associated risks of desaturation.

WEATHERALL EQUIPMENT & INSTRUMENTS LTD

P.O. Box 69, Tring,
Hertfordshire HP23 6PL
Tel. 0494-758110; Fax 0494-758014
Contact: R. H. C. Worthington

Weatherall Equipment are distributors for Riken Keiki gas detecting instruments. The Riken model 18 and IF-18 are widely used for checking the calibration of vaporizers. Working on the principle of the refractive index of a gas, the instruments are sufficiently accurate and simple to operate. The standard instrument is calibrated to read halothane, isoflurane or enflurane on an analogue scale. Alternatively instruments can be calibrated to individual requirements.

THE WELLCOME FOUNDATION LTD

Crewe Hall, Crewe,
Cheshire CW1 1UB
Tel. 0270-629745; Fax 0270-589305
Marketing Manager: Ken Hooper

The Wellcome Foundation Ltd is a research-based manufacturer of Tracrium (atracurium besylate). Tracrium is a highly selective, competitive neuromuscular blocking agent. Used in a wide range of surgical procedures, Tracrium is used in anaesthesia to relax skeletal muscles and facilitate controlled ventilation. It is also suitable for administration by continuous infusion during long surgical procedures. Tracrium is highly suitable for tracheal intubation especially where subsequent muscle relaxation is required.

Each 2.5 ml ampoule contains atracurium besylate 25 mg, the 5 ml ampoule contains 50 mg and likewise the 25 ml ampoule contains atracurium besylate 250 mg. Dose range (i.v. injection) for adults is 0.3–0.6 mg/kg depending on duration of block required. For continuous infusion, the dose range is 0.3–0.6 mg/kg/h.

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Victoria Hospital, Worksop 58
Victoria Infirmary, Glasgow 65
Walsall District General Hospital 61
Walsgrave Hospital, Coventry 61
Walton Hospital, Liverpool 50
Warneford General Hospital, Leamington Spa 61
Warrington District General Hospital 50
Watford General Hospital 55
Waveney Hospital, Ballymena 66
West Cornwall Hospital, Penzance 53
West Dorset Hospital, Dorchester 60
Western General Hospital, Edinburgh 63
Western Infirmary, Glasgow 65
West Middlesex Hospital, Isleworth 55
Westminster Hospital, London 55
Weston-super-Mare General Hospital 53
West Suffolk Hospital, Bury St Edmunds 49
West Wales General Hospital, Carmarthen 63
Wexham Park Hospital, Slough 53
Weymouth & District Hospital 60
Wharfedale Hospital, Otley 62
Whipps Cross Hospital, London 54
Whiston Hospital 50
Whiteabbey Hospital, Newtownabbey 66
Whitehaven Hospital 51
Whittington Hospital, London 54
William Harvey Hospital, Ashford, Kent 56
Withybush General Hospital, Haverfordwest 63
Wolverhampton & Midland Counties Eye Infirmary 61
Woodend General Hospital, Aberdeen 64
Worcester Eye Hospital 60
Worcester Royal Infirmary 60
Wordsley Hospital, Stourbridge 61
Worthing Hospital 57
Wrexham Maelor General Hospital 63
Wrightington Trust Hospital, Ormskirk 52
Wycombe General, High Wycombe 52
Wythenshawe Hospital 52
Yeovil District Hospital 53
York District Hospital 62
Ysbsty Dewi Sant 62
Ysbsty Glan Clywd 63
Ysbsty Gwynedd, Bangor, Gwynedd 62

"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

REGIONAL ANALGESIA AND MYOCARDIAL ISCHAEMIA

Most anaesthetists have encountered the problem of a patient with severe cardiovascular disease placed on the next day's operating list by the surgeon who has told the patient that they will receive regional anaesthesia "as it is safer". However, whilst the physiological and clinical benefits of regional techniques for patients with respiratory disease are well established, their role in patients with cardiovascular disease is less clear. The potential risks of compromising the coronary circulation with sudden hypotension or of precipitating congestive cardiac failure with fluid preloading must be taken into account when making a decision about the anaesthetic technique. What physiological and clinical evidence, therefore, is available to assist the anaesthetist?

The haemodynamic effect of regional analgesia is dependent on the extent of sympathetic nervous system involvement and, hence, on the level of block achieved. A block below L3 does not affect the sympathetic system and the haemodynamic upset is minimal. Haemodynamic changes relate to the extent of involvement of groups of nerves supplying the peripheral vessels, the splanchnic bed (T5–L3) and the heart (T1–4). Block to T10 has a limited effect on the splanchnic bed and vasodilatation occurs mainly in peripheral vessels. However, block to T5 affects both splanchnic and peripheral flow, resulting in a marked decrease in peripheral resistance and a reduction in arterial pressure of at least 25%. In addition, at this level the sympathetic innervation of the adrenals is blocked and this reduces the amount of systemic catecholamines released. This is important, as it is thought that small arterioles respond to humoral rather than neural stimulation and unblocked adrenal output could produce compensatory vasoconstriction. Block of the cardiac sympathetic innervation results in a decrease in cardiac output, slowing of heart rate and decreased contractility. In healthy patients, the effect of this may not be as dramatic as expected, but the effect in a patient with compromised cardiac function would be severe.

Fluid preloading with either crystalloid or colloid has been standard practice for many years. Crystalloid infusion has been shown to produce an increase in circulation blood volume [1]. The value of fluid preloading before spinal anaesthesia in an elderly population has been questioned by Coe and Revanas [2] who found no difference in the incidence of hypotension in patients receiving preloading with Ringer lactate 0, 8 or 16 ml kg^{-1}. The preferential use of vasoconstrictors rather than fluid loading has been advocated in this group of patients [3]. However, in a group of patients with coronary artery disease, the potential for producing tachycardia which is associated with some vasoconstrictors may be undesirable. The most important factor in maintaining good coronary flow is avoidance of rapid changes in either heart rate or arterial pressure.

In a recent review of the prevention and treatment of hypotension associated with regional analgesia, McCrae and Wildsmith detailed the advantages and disadvantages of the various methods of controlling hypotension [4]. Overall, the authors came down in favour of the use of vasopressors in this situation. However, they noted that much of the published work in this area relates to obstetric patients and they highlighted the need for well designed comparative studies of the methods of preventing hypotension.

A haemodynamic study of 10 patients [5] with stable mild angina who received extradural block to a mean level of T9 demonstrated a small increase in left ventricular (LV) ejection fraction and decreased segmental wall motion abnormalities (SWMA) when no fluid load was given. Addition of a fluid load of lactate 500 ml increased the SWMA to near control values. The authors suggested that decreased LV loading was beneficial to myocardial function in these patients. In contrast, a study of 10 patients [6] with coronary artery disease receiving an extradural block to T6–12 with colloid infusion to restore arterial pressure to control values demonstrated a significant increase in SWMA in some patients. The authors attributed this to decreased coronary perfusion as a result of the hypotension which accompanied induction of extradural block.

The benefits of regional analgesia or general anaesthesia in patients with cardiovascular disease has been assessed using various measures of outcome including mortality, postoperative cardiac events (infarction or failure) and more recently the development of myocardial ischaemia. If mortality is taken as a measure of outcome, there is some evidence to suggest that regional analgesia may reduce early postoperative mortality [7]. Most of these data related to hip surgery, and after the initial improvement the long-term outcome was not different [8]. The incidence of postoperative myocardial infarction has been reviewed recently by Mangano [9], who found little evidence to suggest a difference in reinfarction rate between regional and general anaesthesia. However, in a study of general and vascular surgery patients receiving either extradural or general anaesthesia, Yeager and colleagues [10] demonstrated a marked reduction in the incidence of postoperative cardiac failure in the extradural group.

Recent studies of cardiac risk have moved to the detection of perioperative ischaemia which is likely to precede major cardiac events. Ischaemia rates of up to 60% have been demonstrated in patients known to have cardiovascular disease before operation [9]. In this issue, Christensen and colleagues [11] present a small study of 14 "at risk" patients undergoing minor surgery under spinal analgesia who had pre- and postoperative Holter monitoring. They found a high incidence of ischaemia and those patients with preoperative ischaemia tended to have ST segment changes of longer duration and greater severity. In addition, three of seven patients who had no changes before operation developed significant postoperative ST depression. These findings are consistent with those of larger studies of general anaesthesia patients. They are in agreement also with the study by Marsch and colleagues [12], who monitored 51 unselected patients receiving spinal or extradural analgesia for hip surgery. The results of these two studies are interesting, but do not allow us to make the decision between regional and general anaesthesia. What is required are large controlled studies comparing the incidence of perioperative ischaemia and postoperative cardiac events in patients with cardiovascular disease receiving either regional analgesia or general anaesthesia.

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EDITORIAL II

CONSCIOUS LEVELS DURING ANAESTHESIA

In recent years some distinguished psychologists have taken an interest in anaesthesia, which is surely welcome. Consciousness is the most complex phenomenon in the universe and any light shed on it is fascinating, apart from its relevance to everyday anaesthesia. In this issue, Professor Millar [1] has reviewed several studies on therapeutic suggestions under anaesthesia. Similar studies have given contradictory results; he has done much to clarify the issues. His principal theme is that this problem, in common with many other clinically important ones, can only be comprehended adequately in a statistical context—we need to acquire the habit of seeing the facts in that light.

It seems worth pursuing Professor Millar's analysis to include some other studies. Conceivably, a patient's mind can be influenced while he is unconscious, but it seems unlikely—what is surely more plausible is that some patients are not fully unconscious, even when adequately anaesthetized by accepted criteria. Professor Millar considers this possibility, and discounts it because of its rarity; but is partial consciousness during surgery a rarity? Relevant surveys in the U.K. and U.S.A. literature are too small to answer that question. Studies with nitrous oxide, for example, have usually been undertaken in patient populations numbering about 20, which permits only very imprecise predictions: two failures from 20 has 95 % confidence limits from 1 % to 32 %. The only large study with nitrous oxide is that from Bremen [2]; unfortunately it is in German and is not as familiar to English-speaking readers as it deserves to be. In 790 patients breathing 75 % nitrous oxide and no other agent, there were three main findings:

Group 1: Approximately 50 % were unconscious, in the sense that there was no response to verbal contact, even with powerful stimuli.

Group 2: Approximately 50 % were conscious, but in the amnesic–analgesic plane; that is, coherent communication was possible, but the patients felt no pain and had no recall afterwards.

Group 3: Failure was recorded in 2.4 % because pain was felt in some degree and there was recall.

The confidence limits are impressive: groups 1 and 2, 46–54 %; group 3, 1.5–3.7 %.

Thus for nitrous oxide, the position is reasonably clear, but it is much less clear for the commonly used techniques in which nitrous oxide is supplemented with other agents. No large survey has attempted to find the proportion of patients anaesthetized to the amnesic–analgesic plane and there are obvious practical difficulties in doing so. Perhaps the best estimate currently available would be that derived from surveys of anaesthetic failures; we could then make the reasonable assumption that a technique which halves the number of failures is likely to have a similar effect on patients anaesthetized to the amnesic–analgesic plane. Five surveys of the incidence of recall and dreaming in routine anaesthesia have been reviewed recently [3]. In 2466 anaesthetics there were 19 patients with definite recall (0.8 %)—a 3-fold reduction in the failure rate reported in the Bremen study. A similar reduction in amnesic–analgesic patients would correspond to an incidence of 17 %; while 17 % may seem excessively high, it should be noted that 72 % of patients were found to be in the amnesic–analgesic plane in a recent study [4]—the anaesthetic (midazolam–alfentanil) was one used currently in the U.S.A.

For want of better data, let us assume that 17 % is about the correct figure for U.K. techniques. When the true population incidence is 17 %, the sampled incidence, in random samples of 20, is easily predictable from the binomial distribution:

Incidence	Probability	Incidence	Probability
0/20	2 %	4/20	21 %
1/20	10 %	5/20	13 %
2/20	19 %	6/20	7 %
3/20	24 %	7/20	3 %
Sum:	55 %	8/20	1 %
		Sum:	45 %

Thus in 55 % of subjects the incidence would be three in 20 or fewer, whilst in 45 % it would be between four and eight in 20. In the former case it would be hard to demonstrate an effect, because so few of the patients would be in the amnesic–analgesic state; in the latter the opposite would be true. Thus the conflicting results published are what one would predict, if therapeutic suggestions are indeed effective.

Apart from differences between patients, the second main source of variation arises from different techniques. Lighter anaesthesia is used commonly towards the end of surgery, but practice varies greatly. The writer was trained to have the patient awake at the time of tracheal extubation and to use a limited form of therapeutic suggestion at this point—there is a clinical impression that this is beneficial and it seems worth testing.

The logical next step would appear to be to repeat the St Thomas's study [5], playing tapes, not during surgery, but for 10 min after skin closure. During this period, anaesthesia is lightened so that nearly all patients are in the amnesic–analgesic plane. This avoids the need for large samples and would cost very little. A negative result would suggest that further work on therapeutic suggestion is hardly warranted, but a positive result would point to a simple and cost-effective method of improving the quality of everyday anaesthesia.

WIDER IMPLICATIONS

Anaesthetic depth—historical perspective

Anaesthesia for major operations was transformed by the introduction of neuromuscular blocking drugs, which made surgery possible "while keeping the patient in a light plane of anaesthesia" [6]. Recovery was much quicker, safety was improved, long operations in frail patients became possible and untoward effects, such as nausea, were reduced. The only serious disadvantage was a small incidence of awareness during surgery. In minor surgery and short procedures, in which myoneural blockers are not used, the problem has seldom occurred because relatively deep anaesthesia is needed to prevent movement. One MAC is the concentration needed to prevent reflex movement, and is about twice the concentration needed to produce unconsciousness [7]. With neuromuscular block, surgery can be carried out at less than 1 MAC, and this has proved satisfactory in millions of patients. However, as a result of the occasional failure, over the past three decades there has been a tendency to use progressively deeper levels of anaesthesia. This entails some loss of safety but, while there is no completely reliable method of detecting awareness, what alternative is there? The position may change as EEG technology advances [8–10]—if the EEG can indicate when the patient is in the amnesic–analgesic state, the ideal anaesthetic regimen may be realized.

Physical signs

Until then the problem of ensuring adequate anaesthesia remains—the literature on this is vast, so a summary with representative references may be useful. The only certain data about levels of consciousness during surgery come from direct communication with the patient, as John Snow first realized. In short procedures, such as avulsion of a toe-nail, the novice may observe withdrawal of the leg—yet not only is the patient unrousable, but he may remain so for several minutes despite cessation of the anaesthetic. An apparently "purposive" movement has occurred in the absence of consciousness. Snow likened it to movements that occur in natural sleep. Decades later, Sherrington showed that complex, perfectly co-ordinated movements, such as scratching, can occur when conscious control is ruled out because of spinal cord transection.

If reflex activity is clearly no proof of consciousness, what about the opposite proposition: does lack of reflex activity prove unconsciousness? The first difficulty is that complete areflexia requires very deep anaesthesia. For example, Guedel showed that lachrymation persists into plane 3 of stage 3 ether, far deeper than current practice. Is partial reflex suppression a reliable guide? Many attempts have been made to correlate reflex activity with conscious levels. There is, of course, some correlation, but it is far from perfect, with many false positives and negatives [4, 11, 12]. The variable correlation between different autonomic and somatic reflexes is a matter of daily observation in theatre—there is no consensus on which of these spinal functions correlates best with the cerebral function of consciousness; it varies between patients, between agents and between type of stimulus. There are many reports of serious awareness with no warning signs [13–16].

As the only certain data come from direct communication with the patient, may this be used during surgery to test adequacy of anaesthesia? Although good in principle and giving excellent results in some hands [17, 18], it has not proved practicable for general use.

The role of volatile agents

If physical signs are demonstrably unreliable, how is it that modern anaesthesia has a high success rate? This is because reliance is placed mainly on established knowledge of thoroughly tested methods. We know from the Bremen study, for example, that if nitrous oxide is used correctly, that alone guarantees 98% success, even if no attention is paid to physical signs. John Snow reached essentially the same conclusion: "The question may be asked whether the medical man can always determine in what degree of anaesthesia the patient is—I am not sure that he can by mere observation. I have never been deceived, but then I always know the strength of the vapour he is inhaling" [18]. That was based on his first 200 patients, anaesthetized with ether at less than 1 MAC, movement being controlled by manual restraint.

In a larger sample, failures would have occurred. Some failures are caused by technical errors, for which there is no legal defence, but in others this can be ruled out. We suggested [19] that failure might result from a Gaussian distribution of sensitivity to anaesthesia, so that an impeccable anaesthetic, satisfactory in the vast majority, might be inadequate for a few in the upper tail. The Bremen study was the first convincing support for this interpretation.

The next question is whether addition of a volatile agent to nitrous oxide can ensure 100% success and, if so, in what concentration. In obstetric anaesthesia, thiopentone induction followed by unsupplemented nitrous oxide [20] had a failure rate similar to that of the Bremen study. In the follow-up survey [21], 0.5% halothane was added, which reduced the failure rate to 1 in 470. Other studies have claimed 100% success, but the samples were too small—no calculation is needed to see that, in this context, evidence based on samples of 100 or fewer is meaningless. To be significantly better than 3 failures in 1400 (the Glasgow figures [21]), there must be no failures in at least 3200 patients [22, 23].

Benzodiazepines

Volatile agents have proved valuable in supplementing nitrous oxide, but increasing the concentration to guarantee 100% success may endanger some patients because of the relatively narrow margin of safety. With volatile agents, the lethal concentration is only about 3 times the clinical one; in contrast, the therapeutic index of benzodiazepines is very wide. For lorazepam, the LD_{50} in mice is 7000 times the ED_{50} [24]; in man the position seems similar, judging from patients who attempted suicide with vast doses of lorazepam. It is a powerful hypnotic, unlike opioids, and could reasonably be expected to produce unconsciousness in the resistant patient for whom a standard nitrous oxide–volatile combination is not, by itself, sufficient. Clinical experience [25] suggests that this strategy warrants further study.

Against benzodiazepines, it has been argued that they are used so that patients who are aware will not remember it, but that is a misunderstanding—amnesia is an incidental benefit, not the primary objective. The main aim is that explained above. Of course, it is a profoundly uncomfortable thought that a patient we are caring for may suffer without our knowing. One reassuring fact is that a few patients in the amnesic–analgesic plane are not fully amnesic—they recall enough to say they felt no pain. Thus when nitrous oxide is the main agent, pain seems to be abolished before recall, therefore those with no recall can reasonably be taken to be analgesic. The possibility that a patient may be conscious under anaesthesia, and yet have no recall, was demonstrated for ether 150 years ago [18] and has since been confirmed for every anaesthetic—to reject an agent on that ground would imply abandoning general anaesthesia.

CONCLUSION

For the anaesthetist unlucky enough to encounter a serious problem of awareness in a patient, the best defence is that he used a thoroughly tested and documented method and made no technical error, but that defence is seriously weakened if the method was new and based on inadequate samples. Of course research must go on, but to obtain any improvement on current practice, very large sample numbers are required. It follows that future research has to be planned carefully and needs joint work between many anaesthetists, preferably in multi-centre studies. When the climate is hostile to research, combined effort is essential.

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ORIGINAL ARTICLES

MYOCARDIAL ISCHAEMIA AND SPINAL ANALGESIA IN PATIENTS WITH ANGINA PECTORIS

E. F. CHRISTENSEN, P. SØGAARD, K. EGEBO, L. F. BACH AND J. RIIS

SUMMARY

We have studied prospectively myocardial ischaemic events by Holter monitoring of ST-segment depression in patients with angina pectoris given spinal analgesia for minor surgery compared with a reference day of normal daily activities. Monitoring was undertaken continuously for 24 h on both days, starting just before anaesthesia on the day of surgery. On the reference day, seven of 14 patients had 27 ischaemic events with mean max ST-depression of 0.15 mV and total duration of 143 min, compared with 10 of 14 patients with 70 ischaemic events with mean max ST-depression of 0.22 mV and total duration of 1078 min ($P < 0.01$ for all). On the day of surgery, the first ichaemic event occurred a mean 338 min (range 75–480 min) after spinal analgesia, and the duration of all first events was 480 min. On this day, the first ischaemic event was associated with increased heart rate (103 beat min^{-1} (range 66–131 beat min^{-1}) compared with 92 (60–122) beat min^{-1} during all events ($P = 0.011$)). In patients with angina pectoris, myocardial ischaemia did not occur immediately after the onset of spinal analgesia, but several hours later, corresponding to the cessation of block. This could be explained by increased cardiac pre- and afterload, probably further aggravated by the volume load. (Br. J. Anaesth. 1993; **71**: 472–475)

KEY WORDS

Anaesthetic techniques: spinal. Heart: ischaemia. Monitoring: Holter monitoring.

The use of spinal and extradural analgesia in patients with ischaemic heart disease remains controversial. Myocardial ischaemia can be induced or worsened by a decrease in arterial pressure; in contrast, reduction in preload and afterload may decrease cardiac work and myocardial oxygen demand, thereby decreasing the risk of myocardial ischaemia. Myocardial wall motion and function after extradural analgesia have been studied using angiography and scintigraphy [1] and echocardiography [2]. Different results were obtained: Baron and colleagues [1] found that myocardial wall motion improved after extradural analgesia, whereas Saada and colleagues [2] found that myocardial wall motion decreased, indicating ischaemia.

Myocardial ischaemia is the result of imbalance between oxygen requirement and supply. The subendocardium is more prone to ischaemia than the subepicardium; because of a reduction in the reserve capacity of vasodilatation and extrinsic compression during systole, combined with an overall greater metabolic rate. Increased metabolic demand, maldistribution of transmural flow, or both, are responsible for subendocardial ischaemia with subsequent ST-segment deression [3, 4].

During the past decade, a non-invasive method of detecting myocardial ischaemia (continuous electrocardiographic Holter monitoring with subsequent ST-segment analysis) has been developed and standardized [5–7]. Studies have shown that a major part of myocardial ischaemia occurs as silent events in patients with angina pectoris [5], and silent ischaemia has been shown to be a predictor of cardiac morbidity and mortality [6, 7]. Perioperative myocardial ischaemia has been studied in non-cardiac surgery with this method; pre- and postoperative myocardial ischaemia have been revealed to be associated with increased cardiac morbidity in patients with ischaemic heart disease [8–12]. The frequency and duration of myocardial ischaemia during and after spinal analgesia have not been studied.

The aim of this study was to assess perioperative myocardial ischaemia in patients with stable angina pectoris given spinal analgesia for minor surgery, compared with a reference day.

PATIENTS AND METHODS

We studied patients with a history of stable angina pectoris undergoing minor elective surgery or examination under spinal analgesia. All received verbal and written information and gave consent to participate in the study, which was approved by the Ethics Committee of Aarhus. Exclusion criteria were: any contraindication to spinal analgesia, medical treatment (digoxin) and other conditions interfering with ST-segment analysis because of ECG-abnormalities (bundle branch block, left ventricular hypertrophy and strain, or persistent ST-segment depression in the monitored leads).

Monitoring was performed continuously for 24 h during the day of operation and on a reference day of

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This article is accompanied by Editorial I.

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normal daily activities. We used a calibrated, amplitude-modulated, two-channel tape recorder (Reynolds Tracker) fulfilling the specifications of the American Heart Association for detecting ST-segment changes [13]. Either a modified anterior lead (V3) or modified inferior lead (aVF), and a modified lateral lead (V6) were used (the anterior lead was preferred, but if the patient previously had an anterior myocardial infarction the modified inferior lead was chosen). Care was taken during positioning to avoid leads with Q-waves. Each tape contained 24 h of recording and the monitor was applied to the patient just before anaesthesia on the day of surgery. Twenty-four hours of monitoring was performed on a reference day at the patient's home after the day of surgery (at least 3 days later, when daily activities were resumed). ST-segment analysis was performed on both leads and tapes were replayed at 60 times recording speed using a Reynolds Pathfinder 3ST connected to a computer (ST-scope). The analyses were kept under visual observation and trend curves of ST-segment deviation, ST-segment slope and heart rate were generated on the computer screen for the whole of the monitoring period. A myocardial ischaemic event was defined as a horizontal or down sloping ST-segment depression of 0.1 mV or more lasting at least 1 min and measured 80 ms after the J-point. Events had to be at least 2 min apart to be classed as separate episodes. The ECG at events of interest was printed (25 mm s^{-1}) for visual evaluation before final acceptance. The number of ichaemic events, their duration and onset, and maximal ST-segment change and heart rate at onset were noted for each tape.

Anaesthetic procedures

Patients had their usual medication for angina on the morning of the day of operation. Spinal analgesia was performed using a 25-gauge needle at the L3–4 or L2–3 interspace, and "plain" bupivacaine 17.5 mg (Marcain 5 mg ml^{-1}, Astra, Sweden) was injected, after an i.v. infusion of isotonic saline had been commenced. Arterial pressure and heart rate were recorded every 5 min during anaesthesia. The rate of infusion was increased when the systolic pressure decreased 25 % or more from preanaesthetic values, and ephedrine in doses of 5 mg was given, if rapid infusion of saline did not improve the arterial pressure. Segmental spread of sensory loss was tested after 15–30 min. The patients were observed afterwards until sensory block reduced, and the patients were encouraged to mobilize as soon as motor block had disappeared. Most patients were discharged from hospital the day after surgery.

Statistical methods

The Wilcoxon test for paired data was used. Values are given as mean and total range.

RESULTS

We studied 15 patients, but data from only 14 were analysed, as one of the tapes was useless because of technical reasons (table I). Ten patients required daily medical treatment for angina pectoris: four received a beta-blocker; five patients received calcium antagonists; three received long acting nitrates; two were treated with more than one drug.

On the day of surgery, 10 patients had 70 ischaemic events, whereas seven patients had a total of 27 events on the reference day (table II) ($P < 0.01$). During the day of surgery, the total duration of ischaemic events was significantly greater (1078 *vs* 143 min) ($P < 0.01$) and the mean maximum decrease in ST-segment was significantly greater (0.22 *vs* 0.15 mV) ($P < 0.01$) (table II). On the reference day, ischaemic events occurred more frequently in the early morning and late afternoon. Mean heart rate (HR) during the ischaemic events on the reference day was 88 beat min^{-1} (range 83–98 beat min^{-1}), which was not different from mean HR during all events on the day of surgery. The first ischaemic event on the day of surgery occurred a mean 338 (75–480) min after spinal analgesia was performed; none occurred immediately after spinal analgesia. The total duration of all first events was 480 min, which constituted 45 % of the total duration of ischaemic events on the day of surgery. Minimum and maximum duration of first ischaemic event were 3 and 176 min, respectively. Mean HR during the first event was 103 (66–131) beat min^{-1}, which was significantly greater ($P < 0.05$) than the mean HR of 92 (60–122) beat min^{-1} for all events during the day of surgery. No patient complained of chest pain, and no clinical cardiac complications occurred.

On the day of surgery, mean arterial pressures before operation were 111 (range 90–140) mm Hg systolic and 70 (50–90) mm Hg diastolic; mean arterial pressure (MAP) was 83 (range 63–97) mm Hg measured immediately before anaesthesia. The least mean systolic and diastolic pressures after spinal analgesia were 100 (75–120) mm Hg and 65 (50–85) mm Hg, respectively, corresponding to MAP 77 (62–95) mm Hg, which occurred a mean 25 (5–60) min after the preoperative measurement. For the four patients without ischaemic events on the day of surgery (patients Nos 8, 9, 10 and 13), mean systolic and diastolic pressures before operation were 110 (95–110) mm Hg and 70 (60–75) mm Hg, and least mean systolic and diastolic pressures were 95 (75–115) mm Hg and 65 (55–75) mm Hg; there were no differences between the patients with or without ischaemic events on the day of surgery. The least mean HR during operation was mean 55 (45–70) beat min^{-1}, and the greatest was 70 (55–80) beat min^{-1}.

Blood loss was minimal and no blood transfusions

TABLE I. *Details of patients and types of surgery. AMI = Acute myocardial infarction; TURB = transurethral resection of the bladder*

Total patients	14
Sex (M/F)	13/1
Age (yr) (mean (range))	64 (48–84)
Previous AMI (No.)	6
Surgery (No.)	
Orchidectomy	2
Herniotomy	1
TURB	10
Rupture ankle ligament	1

TABLE II. *Myocardial ischaemic events. Total number* (n) *and duration of myocardial ischaemic events, and mean maximal ST-segment depression during the events during 24 h of Holter monitoring.* **P < 0.01 *compared with reference day*

	Reference day			Day of surgery		
Patient No.	*n*	Duration (min)	ST-depression (mV)	*n*	Duration (min)	ST-depression (mV)
1	2	10	0.14	9	293	0.32
2	6	32	0.16	11	140	0.28
3	0	0		2	13	0.18
4	5	25	0.14	13	227	0.20
5	1	1	0.11	9	88	0.15
6	0	0		2	37	0.19
7	0	0		1	4	0.16
8	0	0		0	0	
9	0	0		0	0	
10	0	0		0	0	
11	5	23	0.20	5	55	0.26
12	3	27	0.15	11	159	0.24
13	0	0		0	0	
14	5	25	0.13	7	62	0.23
Total	27	143		70**	1078**	
Mean	2	10	0.15	5**	77**	0.22**

were given. A mean 1575 (1000–3000) ml of isotonic saline and 300 (200–1000) ml of glucose 5.5 mg ml^{-1} was given during anaesthesia and the period of observation after surgery. Six patients (two without ischaemic events (Nos 9 and 10)) and four patients with events (Nos 4, 7, 12 and 14) were given ephedrine: five received 5 mg and one received 10 mg. The sensory blocks ranged from T12 to T2 (T2 in only one patient). The mean total time from arrival in the operating theatre to the departure from the post-anaesthetic care unit was 4 (2.5–5) h. There were no differences between patients with and without ischaemic events on the day of surgery in any of these perioperative aspects.

DISCUSSION

We have found more frequent, longer and more severe silent ischaemic events after spinal analgesia for minor surgery in patients with stable angina pectoris compared with a reference day of normal daily activities. A more surprising finding was that the ischaemic events did not occur in association with the onset of block, with the decrease in MAP after spinal analgesia or with the administration of ephedrine, but that the first event occurred some hours after the application of spinal analgesia. In our study, preoperative MAP was small (less than 100 mm Hg), probably because of medical treatment or the severity of the ischaemic heart disease, and the decrease in MAP was minor. The severity of the disease was reflected also in the high frequency of ischaemic events: 50 % of patients had events on the reference day and 71 % had ischaemic events on the day of surgery. These frequencies are among the greatest reported [9–12, 14], especially because events with ST-elevation were not defined as ischaemic, in contrast with the practice in some of the other studies [10–12, 14]. We considered only ST-depressions, as the subendocardium is more susceptible to ischaemia than the subepicardium [3, 4].

Our study was a paired study comparing the occurrence of ischaemic events in the same patient on the day of surgery and on a reference day, and was not designed to elucidate the differences between patients with and without perioperative ischaemic events. Thus our study did not reveal which factor or factors are the most important concerning development of ischaemic events in association with surgery. However, we did not find significant differences concerning haemodynamics or perioperative management between patients. The first ischaemic event seemed to occur with or after the cessation of analgesic block or when the segmental spread of spinal analgesia was regressing, although we do not have information about the exact spread of block at this time. The events were longer and more severe than on the reference day and, with the late onset, many occurred after the patient had left the post-anaesthetic care unit. There are several possible explanations for the late onset of myocardial ischaemia. At this time, sympathetic nervous block and partial arterial and venous dilatation gradually cease, thereby increasing cardiac pre- and afterload and the work load of the heart. This may be aggravated by the perioperative volume load. In studies on extradural block, different results have been found. In one study [1] extradural block was shown to improve left ventricular wall motion and ejection fraction, whereas the abnormal wall motions reappeared when extradural block was accompanied by volume loading with 500 ml of lactated Ringer's solution. The patients had mild, exercise-induced angina pectoris and none had a history of myocardial infarction. In contrast, in another study lumbar extradural anaesthesia was found to decrease segmental myocardial wall motion in patients with more severe angina pectoris [2], and this occurred simultaneously with a decrease in MAP from 100 (SD 14.9) to 83 (15.5) mm Hg. However, these studies used different methods for evaluating myocardial ischemia.

The duration of the initial ischaemic event on the day of surgery was prolonged, and associated with a significant increase in HR; thus it was probably caused by increased myocardial oxygen demand.

Other studies have different findings on tachycardia and ischaemic events. Fleisher and colleagues [11] found a greater HR after operation, but only 25% of the perioperative ischaemic events were found to be preceded by tachycardia defined as HR > 100 beat min^{-1}. In a study of 108 patients with cardiovascular disease undergoing non-cardiac surgery, 61% of ischaemic events were associated with tachycardia, defined as 10% increase in baseline HR [14]. In the latter study, different anaesthetics were used, including spinal analgesia in 11 patients, but there was no detailed information. In the two studies of extradural anaesthesia, tachycardia did not occur.

It has been said that much of the descriptive phase of research on perioperative myocardial ischaemia is complete, and that it now is important to determine aetiology and design treatment regimens [8]. We agree with the last two statements, but we believe that descriptive studies of spinal and extradural analgesia and ischaemic heart disease are still necessary. More standardization of the anaesthetic procedure, especially sensory and sympathetic block, is needed. Treatment regimens with different procedures for volume loading, the use of diuretics, reduction of heart rate, and anti-angina treatment are important.

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EFFECT OF INTRAOPERATIVE INSPIRED GAS MIXTURES ON POSTOPERATIVE NOCTURNAL OXYGEN SATURATION

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SUMMARY

Continuous postoperative nocturnal pulse oximetry was performed in 20 patients undergoing elective cholecystectomy to examine if the composition of anaesthetic gas mixtures affects postoperative gas exchange. The patients were allocated randomly to receive either nitrogen or nitrous oxide during anaesthesia, and oximetry was performed on the night before operation and the first and third nights after operation. Considerable oxygen desaturation was seen in both groups. During the first night after operation the proportion of the night during which oxygen saturation was less than 85% was greater in the nitrogen group than in the nitrous oxide group, but there was no significant difference between the mean overnight saturation values of the two groups. (Br. J. Anaesth. 1993; **71**: 476–480)

KEY WORDS

Anaesthetics, gases: nitrogen, nitrous oxide. Lung: gas exchange. Monitoring: pulse oximetry. Oxygen: saturation.

It has been known for many years that upper abdominal surgery is associated with an impairment of gas exchange in the lung and that this persists for several days after operation [1–3]. Recent studies using pulse oximetry have shown that many patients have some nocturnal arterial oxygen desaturation for up to 5 nights after operation, and that this is often associated with episodes of obstructive or central apnoea [4].

A major cause of arterial desaturation is believed to be the development of atelectatic areas in dependent zones of the lung. These develop shortly after induction of anaesthesia and persist into the postoperative period [5, 6]. It is believed that the lung changes are associated with the reduction in functional residual capacity (FRC) which occurs on induction of anaesthesia and persists for several days after operation. However, it has also been suggested that anaesthesia with a gas such as nitrous oxide, which has a relatively great blood solubility, may increase the development of atelectasis in alveoli with critically low ventilation:perfusion ratios [7]. This theory is supported by the observation that substitution of nitrogen for nitrous oxide during anaesthesia and thoracotomy for repair of hiatus hernia decreased the magnitude of collapse in the dependent lung as assessed by postoperative radiographs [8].

Because overnight pulse oximetry recording provides more comprehensive data than repeated blood-gas analysis after operation, we decided to use this technique to compare the effects of intraoperative administration of nitrogen or nitrous oxide on the development of nocturnal hypoxaemia after a standardized upper abdominal operation.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. Twenty-three patients scheduled to undergo routine cholecystectomy via a standard transverse right subcostal incision gave informed consent to inclusion in the study and were allocated, according to a randomized order drawn up before the start of the study, to receive either nitrous oxide or nitrogen as a component of their intraoperative inspired gas mixture.

In accordance with Ethics Committee requirements, the patients were free to leave the study at any stage. Of the 23 from whom baseline measurements of oxygen saturation were recorded on the night before operation, 20 (ASA I or II) were studied again on the first night after operation and 11 on the third night (table I).

On the night before operation, the patients were permitted to receive night sedation, if required, in the form of temazepam 10 mg; this was taken by four

TABLE I. *Patient characteristics (No. or mean (SE) [range])*

	Nitrous oxide group	Nitrogen group
No. of patients (M/F)		
First night after op.	9/8	11/10
Third night after op.	5/5	6/5
Age (yr)	62 [38–75]	76 [26–74]
Weight (kg)	76 (6.7) [50–115]	69 (3.5) [52–85]
Past history of cigarette smoking	1	4

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patients. All patients received temazepam 20–30 mg 1 h before operation. One patient was also given pethidine 100 mg i.m. for gall bladder pain.

Anaesthesia was induced with thiopentone 4–5 mg kg^{-1}, fentanyl 1.5–2.5 $\mu g\ kg^{-1}$ and vecuronium 0.1 mg kg^{-1}. All patients underwent manual ventilation of the lungs before tracheal intubation was performed, the nitrogen group receiving 2 % enflurane in oxygen and the nitrous oxide group 2 % enflurane with 68 % nitrous oxide in oxygen. Subsequently, all patients underwent mechanical ventilation of the lungs by a Nuffield 400 ventilator and circle absorber system delivering tidal volumes of 10 ml kg^{-1}; frequency was adjusted to produce an end-tidal carbon dioxide concentration of 4.5 %. All patients received 30 % oxygen and 1–2 % enflurane, depending on depth of anaesthesia and cardiovascular response, plus either nitrous oxide or nitrogen (nitrogen delivered in the form of medical air; oxygen concentration measured with a calibrated fuel cell analyser).

Use of i.v. fluids was standardized as far as possible. One litre of Hartmann's solution was given over the first 1 h and an additional 1 litre over the next 4 h. This was followed by glucose–saline 1 litre over each of the subsequent 8- and 12-h periods. Four patients (three in the nitrogen group) also received Dextran 70 500 ml in normal saline as part of one surgeon's antithrombotic regimen.

All patients received papaveretum 15–20 mg and prochlorperazine 6.25 mg i.m., 5–10 min before the end of the operation. They were then prescribed the same analgesia as required 4-hourly. The last four patients studied (two in each of the study groups) also received 0.5 % bupivacaine 10–20 ml injected into the wound edges during skin closure.

Data collection and analysis

Continuous nocturnal oxygen saturation recordings were made before operation and on the first and third nights after operation, using an Ohmeda 3740 pulse oximeter which measured arterial oxygen saturation (Sp_{O_2}) via a finger probe secured to the patient's finger with an adhesive dressing. Data were stored and analysed using a specially designed computer program running on a Toshiba 1600 computer.

A computer analysis program [9] performed second-by-second sampling of Sp_{O_2} and heart rate and calculated average saturation for the entire duration of the recording, mean values and SD of Sp_{O_2} during each 10- or 30-min epoch and percentage of recording time during which Sp_{O_2} was less than 90, 85 or 80 %.

Whenever the finger probe was detached from the finger, to allow patient mobility, to facilitate nursing intervention or accidentally, zero data points were recorded and automatically rejected from further analysis by the computer program. An average of about 7 % of the potentially available data were excluded in this way.

The mean total duration of overnight recording was 9.8 h, representing 35280 potential items of data. Individual saturation recordings were examined to ensure that those collected were satisfactory. Successive 10-min continuous recordings revealed an overall pattern of reasonably stable oxygen saturation with intermittent, brief periods of desaturation and recovery.

Our computer program did not record signal amplitude. We were therefore unable to measure signal artefact as described recently elsewhere [10]. A small amount of movement artefact was seen in all patients but, given the overall duration of the recordings and number of observations obtained, we assumed this would have had little effect on the mean overnight oxygen saturation or cumulative analysis of overnight oxygen saturation. A visual analysis of the number of periods of transient oxygen desaturation (decreases in oxygen saturation of 4 % or more with prompt recovery of at least 3 %) was made for each overnight recording obtained.

RESULTS

Individual mean overnight oxygen saturations are shown in figure 1. Mean Sp_{O_2} in each patient decreased by 0.9–14.3 % on the first night after operation. The greatest individual overnight mean Sp_{O_2} on the first night after operation was 95.4 % and the least 78.5 %.

Mean overnight oxygen saturation was greater in the nitrous oxide group than in the nitrogen group (ns: Student's t test, $P = 0.05$) (table II). The

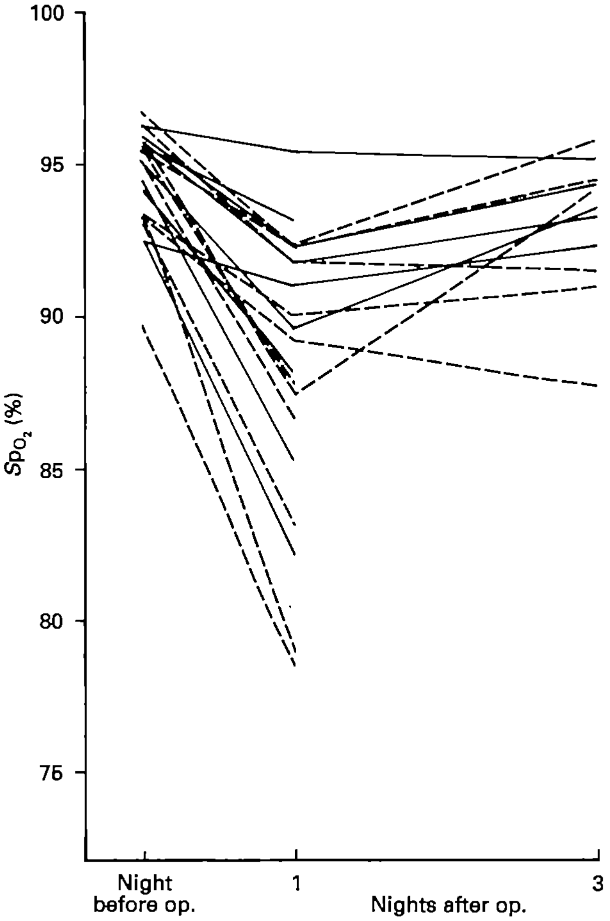

FIG. 1. Individual mean nocturnal oxygen saturation during the night before operation and the first and third nights after operation. —— = Nitrous oxide group; – – – = nitrogen group.

TABLE II. *Mean nocturnal oxygen saturation and percentage of recording when oxygen saturation was less than 90%, 85% or 80% during night before and first and third nights after operation*

Study group	Nocturnal Sp_{O_2} (%) (mean (SE) [range])	Percentage of recording at Sp_{O_2}		
		< 90%	< 85%	< 80%
Night before op.				
Nitrous oxide ($n = 9$)	94.7 (0.5) [92.5–95.9]	6.9	0.2	0.1
Nitrogen ($n = 11$)	94.4 (0.6) [89.7–96.6]	7.8	0.6	0.1
First night after op.				
Nitrous oxide ($n = 9$)	89.9 (1.4) [82.1–95.4]	48.5	15.1	3.2
Nitrogen ($n = 11$)	87.1 (1.5) [78.5–92.4]	68.1	32.6	17.2
Third night after op.				
Nitrous oxide ($n = 5$)	93.7 (0.5) [92.3–95.1]	4.4	0.5	0.1
Nitrogen ($n = 6$)	92.4 (1.2) [87.6–95.7]	27.3	2.9	0.2

nitrous oxide group also showed smaller individual decreases in mean overnight Sp_{O_2}, but again these were not significantly different from those in the nitrogen group (Mann–Whitney, $P = 0.05$).

All patients studied spent a proportion of the first night after operation with Sp_{O_2} less than 85% (table II), but the proportion was greater in the nitrogen group (Mann–Whitney, $P < 0.01$).

Eleven of the 20 patients studied on the first night after operation agreed to an additional recording being made on the third night. Three exhibited further small decreases in mean Sp_{O_2}. In the remaining patients Sp_{O_2} increased, but none fully recovered their preoperative oxygen saturation.

Visual analysis of Sp_{O_2} records revealed a generally stable pattern, with little difference between mean Sp_{O_2} in successive 10-min epochs. However, all patients showed transient periods of oxygen desaturation (sudden decrease of > 4% saturation with prompt recovery of at least 3%) on all three nights of recording. Average numbers of transient desaturations per hour in the nitrous oxide group were 4, 17 and 7 on the preoperative, first and third postoperative nights, respectively; corresponding numbers in the nitrogen group were 4, 21 and 5 (no significant difference between groups; Mann–Whitney, $P = 0.05$).

There was no correlation between age or obesity and degree of postoperative oxygen desaturation, and a past history of cigarette smoking did not influence the degree of oxygen desaturation. Use of incisional bupivacaine or Dextran 70 did not appear to influence the degree of oxygen desaturation.

Postoperative pain assessment was not included in the study design. However, recovery staff received the impression that patients who had received nitrogen awakened in more pain than those who had received nitrous oxide. The nitrogen group as individuals received more papaveretum than those in the nitrous oxide group during the first three 24-h periods after operation (38.6 mg *vs* 33.1 mg; 48.63 mg *vs* 41.67 mg; 26.4 mg *vs* 13.3 mg). Analysis of drug consumption on an mg kg^{-1} basis showed similar results, but the differences were not significant (Mann–Whitney, $P = 0.05$). There was no correlation at a 5% level of significance between the amount of analgesia received and the degree of nocturnal oxygen desaturation (Spearman's rank correlation).

DISCUSSION

All 20 patients studied had smaller nocturnal mean Sp_{O_2} values on the first night after operation than on the night before operation, the decrease in mean Sp_{O_2} ranging from 0.9% to 14.3%. Although this value was smaller in the nitrogen group, the difference was not significant. During the third night after operation, three of the 11 patients studied showed further small decreases in mean Sp_{O_2}, whilst in the remainder Sp_{O_2} had returned towards preoperative values. Patients who received nitrogen spent a significantly greater proportion of their first night after operation with Sp_{O_2} less than 85% than did those who received nitrous oxide.

The mechanisms and time course of postoperative hypoxaemia have been reviewed extensively [4]. It is believed that physiological changes occurring as a consequence of anaesthesia may persist after operation and be modified by postoperative events. This study was designed to examine if the nature of the anaesthetic gas mixture might have any effect on postoperative respiratory function.

It is well known that functional residual capacity (FRC) decreases immediately after the induction of anaesthesia [11]. This is thought to be the result of a reduction in the resting tone of the inspiratory muscles of the rib cage and diaphragm, which normally oppose the intrinsic elastic recoil of the lung tissue. At the level of the alveolus, such a reduction in FRC should produce a reduction in the size of individual alveolar units. On a theoretical basis, this may predispose to alveolar collapse [7]. The likelihood of such collapse occurring should be increased by the presence of gases with high blood/gas solubility coefficients, such as nitrous oxide, leading to "absorption atelectasis", and should be decreased by less soluble gases, such as nitrogen.

This effect was demonstrated clinically in a study which examined the effect of substituting nitrogen for nitrous oxide in the anaesthetic gas mixture given to a group of patients undergoing thoracotomy for hiatus hernia [8]. The investigators found a 51% incidence of radiologically-evident postoperative atelectasis in patients who had received nitrous oxide during this procedure, compared with a 24% incidence in a similar group of patients who were given nitrogen. However, the nitrous oxide patients were studied retrospectively and the nitrogen patients prospectively, so that the two groups may have been affected by other variables. Another study examined the effects of nitrogen and nitrous oxide on venous admixture during anaesthesia in a group of patients undergoing minor surgery [12] for which neither anaesthetic technique nor surgical procedure was standardized. Venous admixture was calculated from measurements obtained during spontaneous or controlled ventilation with 30% oxygen in nitrogen and a fixed difference of oxygen content between arterial and mixed venous blood was assumed. The calculated shunts were compared with those calculated for a group of patients who received oxygen in nitrous oxide and no significant difference in venous admixture during anaesthesia was observed between the two groups.

Both the above studies may be criticized on the grounds that they were not planned as randomized controlled trials, therefore we studied patients subjected to a standardized anaesthetic and operation, the only variable being the administration of nitrogen or nitrous oxide during the operation. Although the number of patients we studied was relatively small, our data failed to confirm the suggestion that ventilation of the lungs with nitrogen decreases the incidence of atelectasis resulting from anaesthesia and surgery. This leads us to conclude that critical ventilation:perfusion collapse and absorption atelectasis are not of major importance during anaesthesia for this type of operation, or that the effects of these mechanisms may be hidden as a result of other factors.

Apart from the sometimes severe desaturation which we observed in patients on the first night after operation, the most surprising aspect of our study was the fact that patients in the nitrogen group tended to have more desaturation than those in the nitrous oxide group—a finding opposite to that expected on theoretical grounds. One possible explanation is that the patients in the nitrogen group seemed to suffer more pain immediately after operation and tended to require more postoperative analgesia than those in the nitrous oxide group. It is recognized that postoperative pain and analgesia affect ventilatory function [13] and it is possible that the increased postoperative pain inhibited deep breathing and re-expansion of collapsed alveoli, or that the increased requirement for opioids produced central respiratory depression. However, there was no statistical correlation between the amount of opioid administered and the degree of oxygen desaturation.

Whereas absorption atelectasis depends, theoretically, on the gaseous content of critically unstable alveoli, a second possible mechanism of producing intraoperative atelectasis might be by a reduction in the forces tending to hold alveoli open, allowing "compression collapse". We have mentioned already that reduction in thoracic cage tone allows intrinsic elastic recoil of the lungs to produce a reduction in lung volume. Other extrapulmonary forces also may influence this process. General anaesthesia has been seen to be associated with a cranial shift in the resting position of the diaphragm [14]. This appears to result from a shift of blood from the thorax and extremities to the abdomen. In addition, the reduction in the resting tone of the diaphragm during anaesthesia allows the contents of the abdominal cavity to exert a pressure gradient on the adjacent lung tissue [5], producing the "compression atelectasis" in dependent regions of the lung which has been demonstrated by computed tomography of the thorax during anaesthesia [15, 16]. These effects would appear to be a consequence of the state of anaesthesia itself and have been shown to be independent of the mode of induction of anaesthesia and the nature of ventilation of the lungs (spontaneous or controlled) [5] although, with controlled ventilation, the changes might be exaggerated by increased intrathoracic pressure.

Another factor which might have an effect on postoperative respiratory function is the nature of the surgery undergone by patients studied. Surgical manipulation of the abdominal contents can have a profound effect on the function of the diaphragm. In certain circumstances, and particularly after gall bladder surgery [17], diaphragmatic dysfunction may occur for 7–10 days after operation [18, 19]. The overriding cause of this dysfunction would seem to be a reduction in phrenic nerve output, since diaphragmatic contractility can be shown to be normal on direct stimulation of the phrenic nerve [20]. It would appear that inhibition of the phrenic nerve occurs as a consequence of the stimulation of unmyelinated splanchnic nerves [21]. The gall bladder and other regions of the gastrointestinal tract are supplied with receptors responding to compression, distension and movement [17]. Mechanical stimulation of the gall bladder may thus produce a selective inhibition of the diaphragm which may continue into the postoperative period. The resultant reduction in diaphragmatic tone could then contribute to the persistence of intraoperative atelectasis.

We conclude that the substitution of nitrogen for nitrous oxide during general anaesthesia for gall bladder surgery does not influence the development of nocturnal arterial oxygen desaturation during the postoperative period.

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British Journal of Anaesthesia 1993; 71: 481–487

CAUSES OF OXYHAEMOGLOBIN SATURATION INSTABILITY IN THE POSTOPERATIVE PERIOD

P. G. ROE AND J. G. JONES

SUMMARY

Healthy, young patients tend to have stable patterns of oxygen saturation (Sa_{O_2}) in the perioperative period, but unstable patterns of oxygen saturation data in the postoperative period have been described which are associated with wide fluctuations in the value of Sa_{O_2} over short periods of time and with a propensity for severe desaturation. This investigation was designed to study the cause of these unstable, hypoxaemic patterns. Sp_{O_2} was measured by pulse oximetry in an "at risk" patient group (n = 20) before and after operation and displayed as sequential distribution diagrams and centile plots. In 16 of these patients Sp_{O_2} was determined also at different values of PI_{O_2} (21–50 kPa) before and after operation. Instability of Sp_{O_2}, assessed over periods of 1 h, was common (n = 18) after operation; it was caused by both acute desaturations and a fluctuating baseline Sp_{O_2}. The PI_{O_2} vs Sp_{O_2} relationship was displaced after operation, with both lateral (rightwards) and downwards displacement. The result was to bring the PI_{O_2} to or near to the steep part of the curve. In patients who displayed an unstable pattern of Sp_{O_2} over a short period of time (< 5 min), this was abolished by increasing PI_{O_2}. We postulate that the displacement of the PI_{O_2} vs Sp_{O_2} curve increases the propensity to desaturation in those patients with impaired control by placing the steep part of the curve near to a PI_{O_2} value of 21 kPa. (Br. J. Anaesth. 1993; **71**: 481–487)

KEY WORDS

Complications: hypoxaemia. Oxygen: oxyhaemoglobin saturation.

Continuous measurement of oxygen saturation in the postoperative period using pulse oximetry has been used in many studies [1–4]. We have described previously patterns of oxygen saturation measured continuously in the perioperative period in patients after lower abdominal [2] and thoracic [3] surgery using sequential distribution diagrams. While many patients show a stable pattern of oxygen saturation, others show very unstable patterns characterized by a wide distribution of oxygen saturation with considerable variation from hour to hour. The nature and cause of this instability is unknown, but it has been shown to occur at night [2] and in association with i.m. and intrathecal opioids [2, 3]. The factors most likely to be involved are obstructive apnoea and impaired gas exchange, but their relative contribution is unknown. To investigate this further, we have measured oxygen saturation (Sp_{O_2}) by pulse oximetry continuously in the pre- and postoperative periods in a group of patients at increased risk of hypoxaemia. In addition, we have determined the relationship between inspired oxygen partial pressure (PI_{O_2}) and oxygen saturation before operation and at intervals after operation; this relationship reflects the shape of the oxygen dissociation curve, but is displaced by the inspired-to-alveolar difference for oxygen and by impaired gas exchange. It was suspected that the propensity for desaturation would be determined by the proximity of PI_{O_2} to the steep part of this curve. The aim of the present study was to describe the nature of unstable Sp_{O_2} in the postoperative period and of changes in the PI_{O_2} *vs* Sp_{O_2} relationship which may be related to this instability.

PATIENTS AND METHODS

We studied a heterogenous group of 20 patients (mean age 52 yr (range 26–82 yr)) undergoing major upper abdominal surgery, many of whom were obese (mean weight 73 kg (range 45–139 kg)) (table I). Ethics Committee approval and informed consent were obtained. No attempt was made to standardize patient selection or anaesthetic or postoperative analgesia, as the aim was to observe current practice in a patient group which might be expected to display a high incidence of postoperative hypoxaemia because of their increased weight and the major nature of the surgery.

Continuous monitoring of oxygen saturation was recorded overnight before operation and for 48 h after operation, using an Ohmeda Biox 3700 pulse oximeter interfaced with an IBM-compatible portable microcomputer. Self-adhesive wraparound disposable finger probes were used, which we have found to have a decreased incidence of movement artefact and to be easier to keep in place over a prolonged period of monitoring. The index finger was used in all subjects as this has been shown to be the most reliable site [5, 6]. The computer collected 30 saturation data items from the oximeter every

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TABLE I. *Details of patients in the study.* Sp_{O_2} *after operation = median of 5 min of oximetry 1 h after operation*

Patient No.	Sex	Age (yr)	Weight (kg)	Operation	Analgesia	Sp_{O_2} (%) Before op.	After op.
1	F	47	54	Colectomy	Extradural	96	91
2	F	57	65	Laparoscopic cholecystectomy	I.v. opioid infusion	96	91
3	F	57	68	Gastric augmentation	Extradural	97	93
4	F	36	126	Gastric stapling	PCAS	94	Vent.
5	M	78	55	Gastrectomy	Spinal catheter	96	91
6	F	36	115	Gastric stapling	I.v. opioid infusion	93	90
7	M	—	—	Laparotomy	Spinal catheter	95	93
8	F	26	50	Ileal pouch formation	Extradural	98	95
9	F	74	50	Colectomy	I.v. opioid infusion	91	85
10	F	39	55	Terminal ileum resection	Spinal catheter	95	93
11	M	36	127	Gastric stapling	Extradural	95	88
12	F	34	90	Gastric stapling	Extradural	97	94
13	F	34	48	Ileal pouch formation	Extradural	97	93
14	F	37	53	Colectomy	Extradural	98	95
15	F	65	50	Oesophagectomy	Extradural	96	96
16	F	61	62	Anteroposterior resection of rectum	Extradural	95	92
17	F	82	56	Anterior resection	Spinal catheter	95	91
18	F	48	139	Gastric stapling	Extradural	95	87
19	M	60	80	Partial hepatectomy	Extradural	—	86
20	M	81	45	Gastrectomy	Extradural	96	93

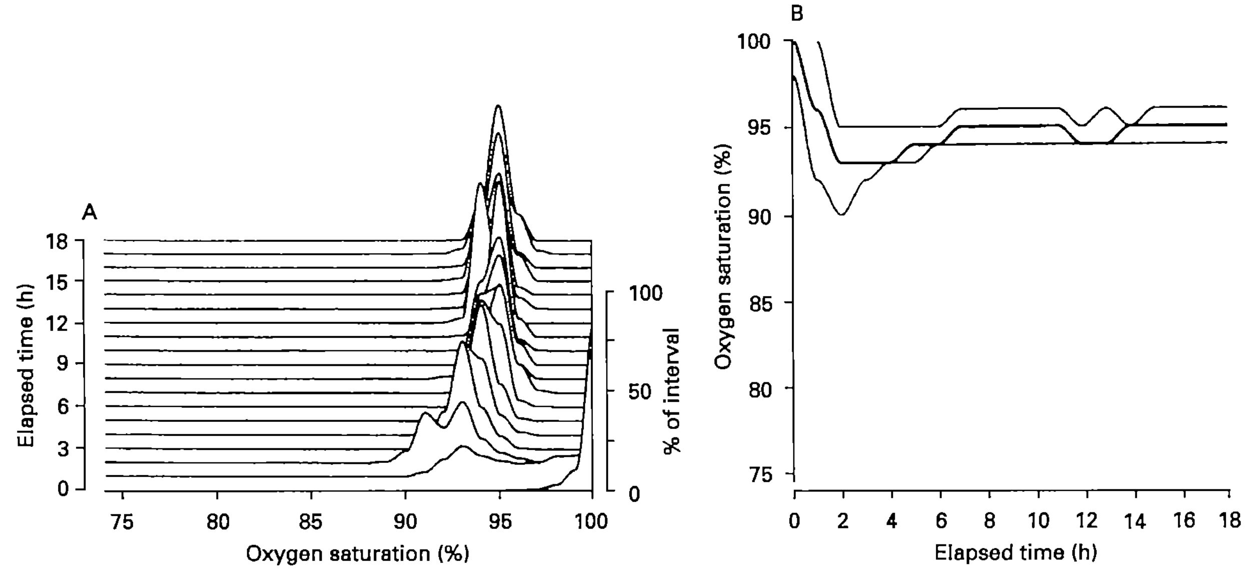

FIG. 1. Continuous oximetry for 18 h after operation in a patient with a stable trace. A: Plot of sequential distribution diagrams of oxygen saturation with intervals of 1 h. B: Centile plot of the same data showing the 5th, 50th (bold) and 95th centile calculated over 1-h intervals. PI_{O_2} was 35 kPa in the first 1 h and 21 kPa (air) thereafter.

1 min; these were stored on 9-cm disks. The data-processing software was able to recognize and store poor signal messages from the pulse oximeter and these could be displayed subsequently. Data processing was carried out using "sequential distribution diagrams" described previously [2, 3], with 1-h data collection intervals (figs 1A, 2A), and "centile plots" which display the 5th, 50th and 95th centile of the Sp_{O_2} data calculated for each 1-h interval (figs 1B, 2B). Poor data were not included. Sections of the data were then plotted as sequential distribution diagrams with 2-min intervals (fig. 3) and as plots of raw saturation data *vs* time.

In 16 of the 20 patients, the relationship between inspired oxygen partial pressure (21–50 kPa) and oxygen saturation was measured before operation, 1 h after operation on return to the ward and at intervals thereafter. Oxygen-enriched air was given via a tightly fitting Ventimask. Inspired oxygen partial pressure (PI_{O_2}) was measured using a Datex Oxycap calibrated against known gas mixtures, which sampled via a cannula taped just in front of the patient's lips. The inspired oxygen was increased from 21% (air) in increments to 50%. A period of 5 min was allowed at each inspired oxygen concentration to permit equilibration. Continuous oximetry was carried out at each increment for a further 5 min to assess for stability. All of these measurements were carried out by one author (P.G.R.). If an apparently unstable set of Sp_{O_2} readings occurred, the probe was tried at different sites and the signal strength, quality of plethysmogram and probe place-

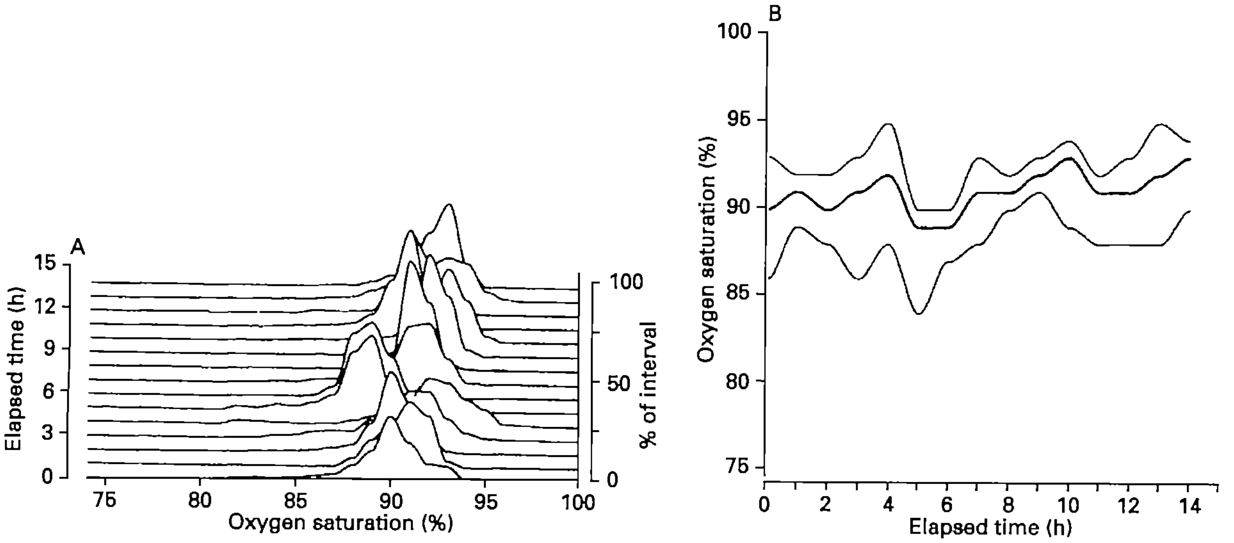

FIG. 2. Continuous oximetry for 14 h on the sixth night after operation in a patient with an unstable trace. A: Plot of sequential distribution diagrams of oxygen saturation with intervals of 1 h. B: Centile plot of the same data showing the 5th, 50th (bold) and 95th centile calculated over 1-h intervals. $P_{I_{O_2}}$ was 21 kPa (air) throughout.

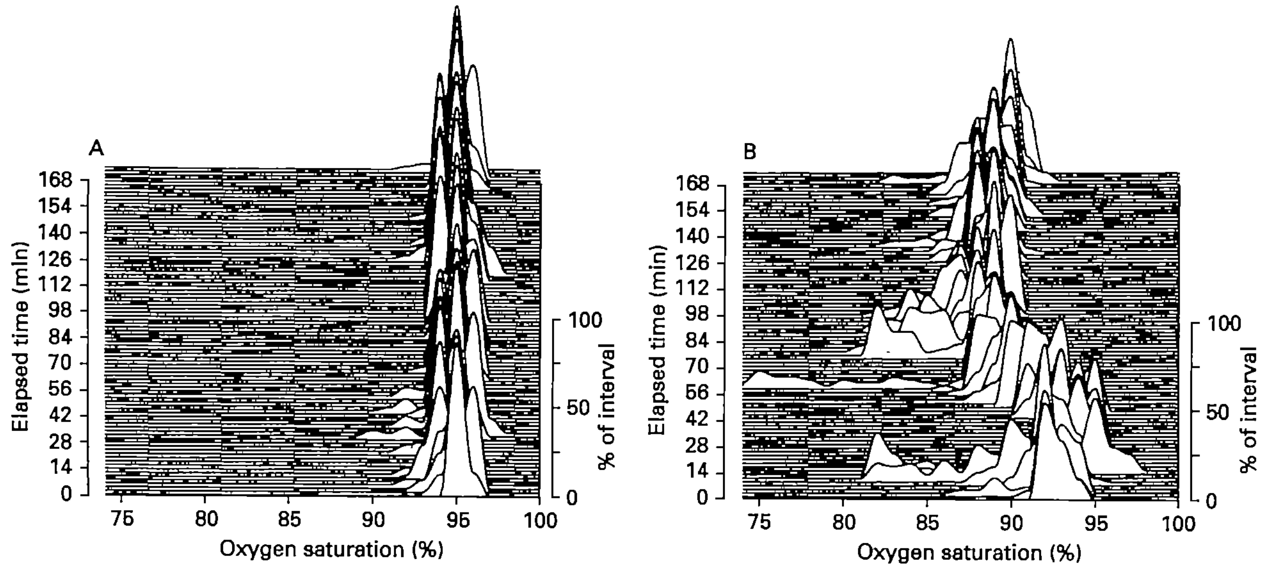

FIG. 3. Details from the stable trace shown in figure 1 (A), and from the unstable trace shown in figure 2 (B). Both plots are for 3 h of data and are plotted as "sequential distribution diagrams" with intervals of 2 min. The unstable trace consists of both acute desaturations and a wandering baseline saturation.

ment were also checked. If it was considered that, as far as possible, a reliable reading of the patient's Sp_{O_2} was being obtained, a minimum of 5 min of data were collected onto computer disk for later analysis. The pulse plethysmogram and the probe site were observed during this time to enable artefacts to be recognized.

The attending staff were free to prescribe oxygen at their discretion. All patients were returned to the ward breathing air and many subsequently were prescribed oxygen as a result of the study.

RESULTS

Oxygen saturation data before and 1 h after operation, taken at the time of determination of the $P_{I_{O_2}}$ *vs* Sp_{O_2} curves are shown in table I. All were measured with a $P_{I_{O_2}}$ of 21 kPa; in the case of unstable traces, the median is given. The mean difference between pre- and postoperative oxygen saturation was 3.89% (range 0–8%).

Two patients displayed predominantly stable traces in the postoperative period; on the sequential distribution diagrams these are characterized by tall, well-superimposed peaks. Using the centile plots, we defined stability as a 5th–95th centile range of < 3% over 1 h with the 50th centile not altering by more than ±1% over a 6-h period (fig. 1B).

Eighteen patients displayed "unstable" patterns in the postoperative period. This was particularly prominent in patients undergoing vertical gastric stapling for morbid obesity. Unstable patterns on sequential distribution diagrams were characterized by wide peaks with much variation from interval to interval. In figure 2B (unstable trace) the 5th–95th centile range is > 3% for 12 of the 14 1-h intervals.

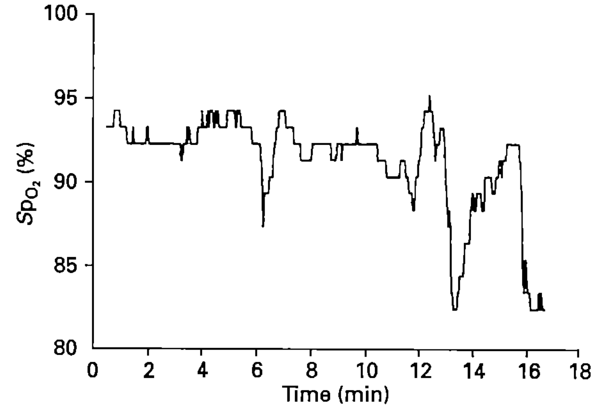

FIG. 4. Plot of Sp_{O_2} against time for the first eight intervals (16 min) of figure 3B. Note how the instability here was caused by discrete desaturations.

In addition, the 50th centile ranges from 89 %, where it lies for two consecutive intervals (5 and 6 h) to 93 % where it lies at 10 h and 14 h.

In order to observe the nature of the instability in these traces, they were re-plotted using 2-min intervals (60 data items per interval). Figure 3 shows examples from the part of the data shown in figures 1 and 2 for both the stable and the unstable pattern. Figure 3B shows two features common to all unstable traces studied: a relatively stable background saturation (tall peaks which tend to superimpose) which drifts slowly over a period of hours; and phasic bursts of instability. In this obese patient breathing air, six nights after operation, obstructive apnoea was observed to be occurring (snoring with paradoxical chest wall/abdominal movements). There were discrete desaturations associated with the observed obstruction. Figure 4 shows the raw saturation data for the first 16 min of this period of observation and corresponds to the first eight curves of figure 3B. Note here how the wide spread of oxygen saturation data noted in the sequential distribution diagrams is caused by these discrete desaturations. Figure 3 also shows how an otherwise stable baseline saturation may shift over periods of 30 min. Both of these features contribute to the instability noted over intervals of 1 h.

Figure 5 shows four representative curves of PI_{O_2} *vs* Sp_{O_2} from patients in whom Sp_{O_2} was stable over a short (5-min) period such that a quasi-static relationship between PI_{O_2} and Sp_{O_2} could be constructed. Note how the postoperative curves become displaced from those obtained before operation.

In seven of the 16 patients in whom the relationship between PI_{O_2} and Sp_{O_2} was determined, short-term instability occurred in the early postoperative period. In one patient this was clearly caused by obstructive apnoea, but in others this instability occurred whilst awake. Four representative curves of PI_{O_2} *vs* Sp_{O_2} showing this phenomenon are shown in figure 6. The oxygen saturation data are expressed as 5th, 50th and 95th centiles. Note how this instability improved as PI_{O_2} was increased. A further example is shown in figure 7 in

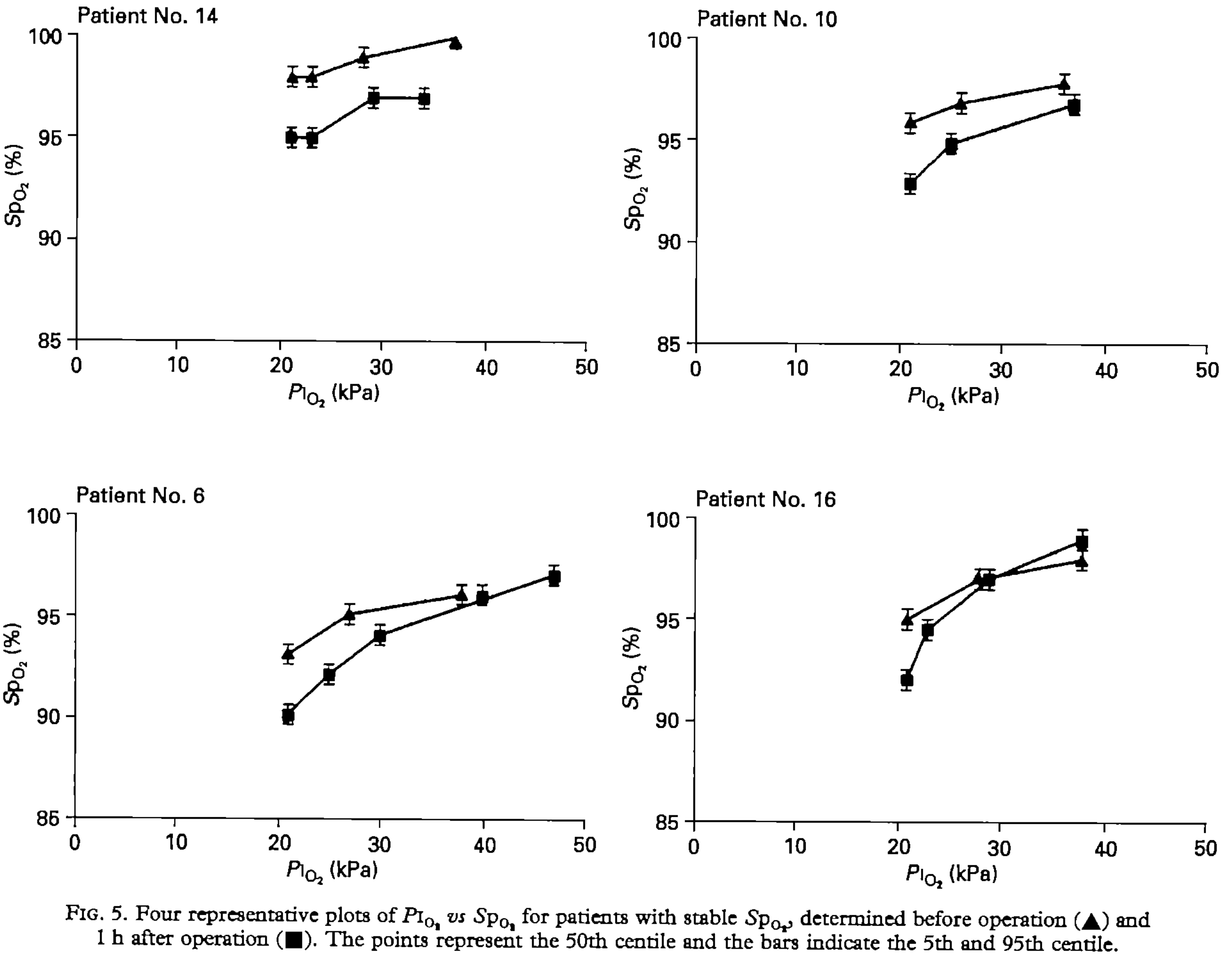

FIG. 5. Four representative plots of PI_{O_2} *vs* Sp_{O_2} for patients with stable Sp_{O_2}, determined before operation (▲) and 1 h after operation (■). The points represent the 50th centile and the bars indicate the 5th and 95th centile.

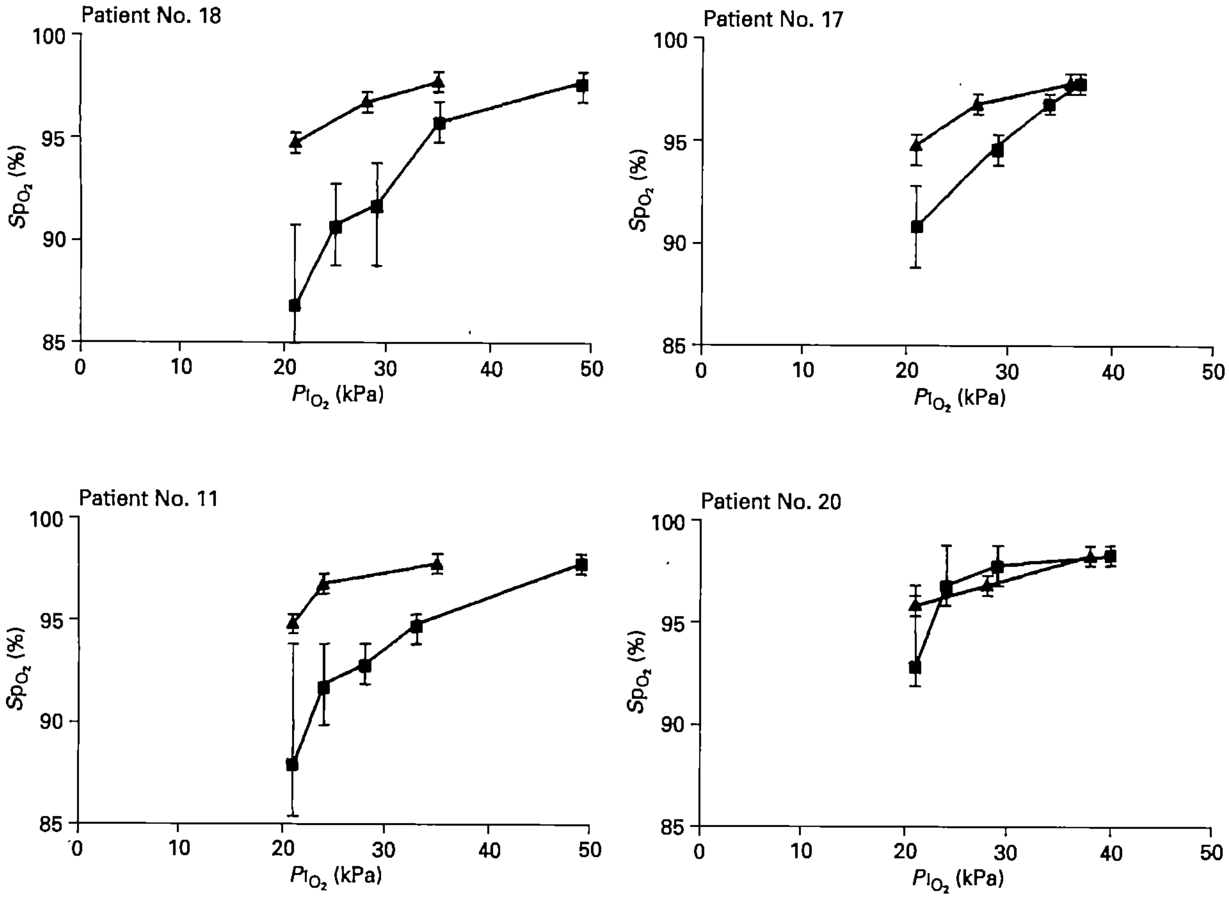

FIG. 6. Four representative plots of $P\mathrm{I}_{\mathrm{O}_2}$ *vs* $S\mathrm{p}_{\mathrm{O}_2}$ for patients with unstable $S\mathrm{p}_{\mathrm{O}_2}$, determined before operation (▲) and 1 h after operation (■). The points represent the 50th centile and the bars indicate the 5th and 95th centile.

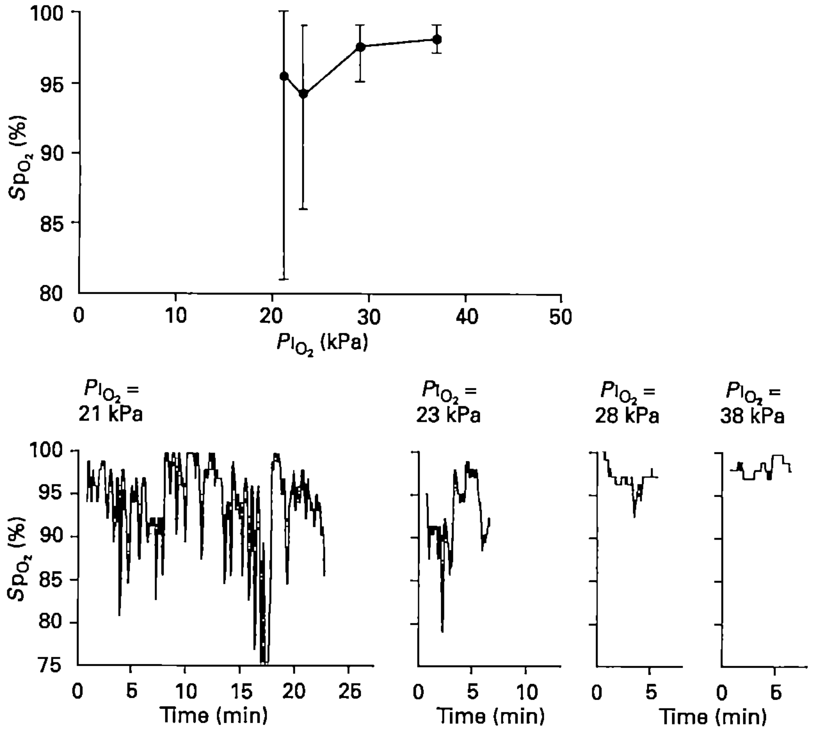

FIG. 7. Top: Plot of $P\mathrm{I}_{\mathrm{O}_2}$ *vs* $S\mathrm{p}_{\mathrm{O}_2}$ for a patient (No. 13) with very unstable $S\mathrm{p}_{\mathrm{O}_2}$, determined 1 h after operation. This patient was asleep and had an irregular ventilatory frequency, but his airway was not obstructed. Below: Plots of $S\mathrm{p}_{\mathrm{O}_2}$ *vs* time for each of the values of $P\mathrm{I}_{\mathrm{O}_2}$.

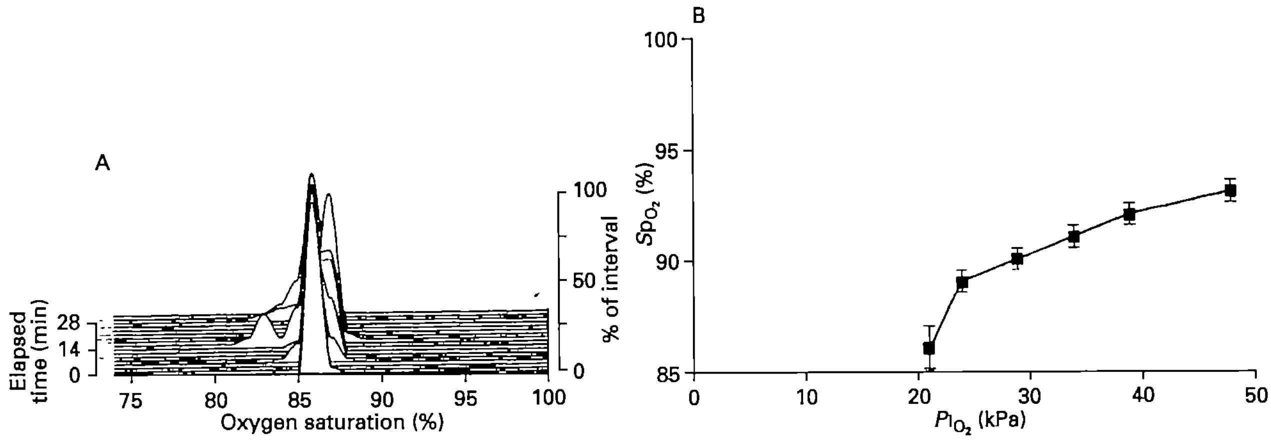

FIG. 8. A: Sequential distribution diagram of oxygen saturation with intervals of 2 min for a patient 1 h after hemi-hepatectomy. Note the stability of this trace at a saturation of 86 %. B: Plot of $P\mathrm{I}_{O_2}$ *vs* $S\mathrm{p}_{O_2}$ for the patient shown in A. Note how this curve is flat compared with those in figure 6.

which, for each of the four values of $P\mathrm{I}_{O_2}$, the plot of raw saturation data *vs* time is given to show the extreme instability displayed by this patient at decreased $P\mathrm{I}_{O_2}$.

Figure 8 shows data from a patient 1 h after tracheal extubation following hemi-hepatectomy. Chest x-ray revealed right lower lobe collapse. Note how the relatively flat $P\mathrm{I}_{O_2}$ *vs* $S\mathrm{p}_{O_2}$ curve is associated with a stable sequential distribution diagram using 2-min intervals.

DISCUSSION

In this paper we describe postoperative hypoxaemia in terms of the stability of the $S\mathrm{p}_{O_2}$ trace and in terms of the position of the $P\mathrm{I}_{O_2}$ *vs* $S\mathrm{p}_{O_2}$ relationship. A major new finding was that the $P\mathrm{I}_{O_2}$ *vs* $S\mathrm{p}_{O_2}$ relationship became displaced in the postoperative period. Downwards displacement was common and was demonstrable even in the patients who displayed short-term instability of oxygen saturation during the construction of the $P\mathrm{I}_{O_2}$ *vs* $S\mathrm{p}_{O_2}$ plots (fig. 6). It is possible that a lateral, rightwards displacement of the $P\mathrm{I}_{O_2}$ *vs* $S\mathrm{p}_{O_2}$ relationship may have occurred in some of the traces (fig. 5; fig. 6). This would bring the steep part of the curve to or near to a $P\mathrm{I}_{O_2}$ of 21 kPa.

The dependence of short-term instability on $P\mathrm{I}_{O_2}$ is also an important finding, as it may be related to alterations in the position of the $P\mathrm{I}_{O_2}$ *vs* $S\mathrm{p}_{O_2}$ curve.

The time course and patterns of postoperative hypoxaemia are now well described [1–4], but the significance of postoperative hypoxaemia and its treatment has been the subject of some debate [7, 8]. Serious hypoxaemia ($S\mathrm{a}_{O_2} < 80\,\%$) is associated with "unstable" patterns which tend to occur at night and are related to sleep and opioid administration. Ventilatory disturbances are associated frequently with profound and potentially life-threatening hypoxaemia in patients with sleep apnoea syndrome [9]. Following anaesthesia and surgery, there is frequently a background of hypoxaemia caused by dependent lung atelectasis [10], upon which respiratory disturbance may result in desaturation. The acute episodic desaturations described in the postoperative period by Catley and colleagues [1] correlated with obstructive apnoea or paradoxical breathing during sleep and never occurred in awake patients. The most common ventilatory disturbances seen in their study were episodes of central apnoea, but these were never associated with desaturation even though they were often of longer duration than periods of obstructive apnoea.

In the present study, one patient was observed with intermittent obstruction during sleep on the night before operation and acute episodic desaturation occurred as a direct result of these obstructions during a 30-min period of observation. A different patient was also observed to be undergoing obstructive apnoea with desaturations on the sixth night after operation. We have no information on the cause of instability during unattended monitoring, but all patients were observed for a period of at least 30 min during the recording of long-term saturation. Instability also occurred in patients who were not undergoing obstructive apnoea. In these patients, a wandering of the baseline pattern was observed when the sequential distribution diagrams were re-plotted with intervals of 2 min. In all patients in whom short-term instability of saturation occurred, this was observed with the patient awake and with no apparent airway obstruction. There was constant observer attendance during these observations to obtain data for the construction of $P\mathrm{I}_{O_2}$ *vs* $S\mathrm{p}_{O_2}$ curves. This short-term instability was related to the $P\mathrm{I}_{O_2}$.

There appear to be two aspects to instability which are observable in the sequential distribution diagrams with 2-min intervals: acute episodic desaturations and a wandering baseline (fig. 3B). Both of these contribute to the wide curves seen in the sequential distribution diagrams with 1-h intervals. In all patients studied who displayed instability, this disappeared when $P\mathrm{I}_{O_2}$ was increased. There are several possible explanations for this phenomenon. First, at increased $P\mathrm{I}_{O_2}$, the oxygen stores in the functional residual capacity allow apnoea to persist for a longer period before desaturation occurs. Against this is the fact that, apart from the two obstructive episodes mentioned above, we never observed apnoea in patients with unstable traces, and Catley and colleagues [1] never associated central apnoea with desaturation. A second possibility is that a rightwards displacement of the $P\text{I}_{\text{O}_2}$ *vs* $S\text{p}_{\text{O}_2}$ relationship has occurred. This results either in an increased proximity of the steep part of the curve to a $P\text{I}_{\text{O}_2}$ of 21 kPa, increasing the propensity to desaturate or, if a sufficient displacement occurs, in the steep part of the curve lying over a $P\text{I}_{\text{O}_2}$ of 21 kPa. Such a rightwards displacement of the $P\text{I}_{\text{O}_2}$ *vs* $S\text{p}_{\text{O}_2}$ relationship can be explained by an increase in the $P\text{I}_{\text{O}_2}-P\text{A}_{\text{O}_2}$ difference which would occur with reduced alveolar ventilation ($\dot{V}\text{A}$). A reduction of $\dot{V}\text{A}$ from 4 to 2 litre min^{-1} would be sufficient to cause this effect.

Small changes in $P\text{I}_{\text{O}_2}-P\text{A}_{\text{O}_2}$ cause large changes in $S\text{a}_{\text{O}_2}$ on the steep part of the curve and these changes would probably be the result of disturbances in respiratory control that occur in the postoperative period. It can be seen that the "*in vivo*" $P\text{I}_{\text{O}_2}$ *vs* $S\text{p}_{\text{O}_2}$ relationship, in contrast to the static relationship between $P\text{a}_{\text{O}_2}$ and $S\text{a}_{\text{O}_2}$ measured "*in vitro*" in a tonometer (oxyhaemoglobin dissociation curve), is a dynamic phenomenon dependent upon changes in $P\text{I}_{\text{O}_2}-P\text{A}_{\text{O}_2}$ and allowing amplification of instability at smaller values of $P\text{I}_{\text{O}_2}$.

The accuracy of pulse oximetry is reduced at small saturations (notably $< 80\%$) [5], and this may account for some instability in the trace. However, the stable hypoxaemic patterns seen in patients whose values were not on the steep part of the curve (fig. 8) argue against this being a major effect at the saturations we studied. In the patients with regional analgesia, it is possible that compensatory vasoconstriction could affect the results [11]. However, during the periods of observed oximetry 1 h after operation, good signal strength and pulse plethysmograms were present. The index finger has been shown to be the most reliable site for measurement in the presence of vasoconstriction [5].

The movement into the clinical range of the steep part of the $P\text{I}_{\text{O}_2}$ *vs* $S\text{p}_{\text{O}_2}$ curve, which is a new finding, is of great clinical significance. Knowledge of the position of this curve and its behaviour in the perioperative period will aid the rational use of oxygen therapy, may enable hypoxaemia to be predicted and may facilitate non-invasive measure of gas exchange impairment.

The consideration of oxygen saturation at differing values of $P\text{I}_{\text{O}_2}$ is similar to the consideration of oxygen partial pressure at differing $P\text{I}_{\text{O}_2}$ in terms of shunt isopleths [12]. It is possible to reconstruct these isopleths in terms of oxygen saturation. We have constructed a theoretical model of both shunt and ventilation–perfusion abnormality and investigated the effect of these and other factors on the shape and position of the $P\text{I}_{\text{O}_2}$ *vs* $S\text{p}_{\text{O}_2}$ relationship. This will be described fully in the accompanying paper [13].

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ANALYSIS OF FACTORS WHICH AFFECT THE RELATIONSHIP BETWEEN INSPIRED OXYGEN PARTIAL PRESSURE AND ARTERIAL OXYGEN SATURATION

P. G. ROE AND J. G. JONES

SUMMARY

The adoption of pulse oximetry in anaesthesia and intensive care has resulted in oxyhaemoglobin saturation (Sa_{O_2}) becoming an important and widely used clinical descriptor of gas exchange, although its full potential has not been realized. We have explored the effect of impaired gas exchange on the relationship between PI_{O_2} and Sa_{O_2}. A curve of oxygen content vs PI_{O_2} for an ideal lung was constructed using the oxygen dissociation curve and allowing for the effect of dissolved oxygen in plasma. A plot of PI_{O_2} vs Sa_{O_2} was derived from this content curve. The effect of impaired gas exchange (shunt and $\dot{V}/\dot{Q}$ effects) on this relationship was then modelled using for shunt the equation $\dot{Q}s/\dot{Q}t = (Cc'_{O_2} - Ca_{O_2})/(Cc'_{O_2} - C\bar{v}_{O_2})$ and for $\dot{V}/\dot{Q}$, a graphical method using the equation $\dot{V}/\dot{Q} = k(Cc'_{O_2} - C\bar{v}_{O_2})/(PI_{O_2} - PA_{O_2})$ and the oxygen content curve to model the effect of a spread of $\dot{V}/\dot{Q}$ ratios. A total of nine compartments were used to model the scatter of $\dot{V}/\dot{Q}$, and the size of these compartments were determined by their relative blood supply. Plots of PI_{O_2} vs Sa_{O_2} were derived for different values of shunt and $\dot{V}/\dot{Q}$. The PI_{O_2} vs Sa_{O_2} curve reflected the shape of the oxygen dissociation curve but lay to the right by $PI_{O_2} - PA_{O_2}$. Shunt caused a depression of the plateau of this curve with relatively little lateral movement, whereas a low mean $\dot{V}/\dot{Q}$ ratio caused a marked rightwards lateral displacement. Increased $\log_{SD}$ $\dot{Q}$ caused a flattening of the relationship. The combined effect of shunt and a spread of $\dot{V}/\dot{Q}$ ratios caused both lateral and vertical displacements. Thus a series of simple measurements of PI_{O_2} and Sa_{O_2} gave information about both shunt and $\dot{V}/\dot{Q}$ abnormality. (Br. J. Anaesth. 1993; **71**: 488–494)

KEY WORDS

Oxygen: oxyhaemoglobin saturation, tension.

In an accompanying paper [1] we showed that the curve relating inspired oxygen partial pressure (PI_{O_2}) and oxyhaemoglobin saturation (Sa_{O_2}) varies considerably in the perioperative period, and that when PI_{O_2} lies on the steep part of the curve the particular patient is at increased risk of postoperative hypoxaemia and likely to display an unstable pattern of Sa_{O_2}. The position and shape of this curve is likely to be altered by factors causing impaired gas exchange and hence it could be used as a non-invasive indicator of such factors, and a predictor of postoperative hypoxaemia. However, there has been no published analysis on how the curve may be affected by such changes. The purpose of this paper is to examine the effect of impaired gas exchange on the PI_{O_2} *vs* Sa_{O_2} relationship using a theoretical model which incorporates shunt and distributions of ventilation/perfusion ratios ($\dot{V}/\dot{Q}$).

Various models have been described in an attempt to understand the physiology of impaired gas exchange. One is that of Riley [2], in which the lung is described in terms of three compartments: shunt, ideal alveoli and deadspace. In this model, units of different ventilation/perfusion ratio ($\dot{V}/\dot{Q}$) are rationalized into varying contributions to the three compartments. Using the Riley model, a value for shunt can be calculated for a given $\dot{V}/\dot{Q}$ abnormality. However, it has also been suggested that the amount of shunt attributable to a spread of $\dot{V}/\dot{Q}$ varies with PI_{O_2} [3, 4]. Multiple inert gas elimination techniques have been used to estimate $\dot{V}/\dot{Q}$ distribution scatter [5] and we have used distributions similar to those derived using this technique to illustrate the working of our model.

THEORETICAL ANALYSIS

We have developed a simple model of $\dot{V}/\dot{Q}$ scatter involving nine compartments: true shunt ($\dot{V}/\dot{Q} = 0$), spread of $\dot{V}/\dot{Q}$ ratios (0.1, 0.3, 0.5, 1, 2, 4, 10) and deadspace ($\dot{V}/\dot{Q}$ = infinity). This modelling in terms of true shunt, $\dot{V}/\dot{Q}$ distribution and deadspace uses compartments (albeit fewer) similar to those used in multiple inert gas elimination techniques. The size of each compartment in the model is variable and is determined by the percentage of the total blood flow to that compartment. When using data from multiple inert gas studies, the multiple compartments were rationalized into those of our model.

We assumed the following values in the model: haemoglobin concentration 15.27 g dl^{-1}; oxygen combining power of haemoglobin 1.31 ml g^{-1}; physical solution of oxygen in blood 0.0225 ml dl^{-1} kPa^{-1}; dry barometric pressure 93.7 kPa, cardiac output 5 litre min^{-1}; oxygen consumption 250 ml min^{-1}. This results in an arterial to mixed venous oxygen

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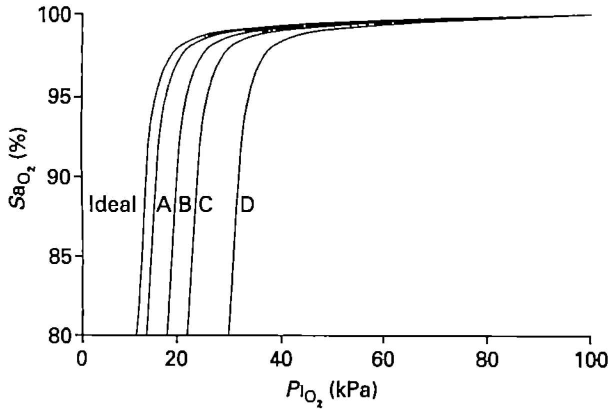

FIG. 1. Inspired oxygen partial pressure *vs* oxyhaemoglobin saturation. The ideal curve shows the relationship where $\dot V/\dot Q = 1$ and $\dot V\mathrm{A} = 4000\ \mathrm{ml\ min^{-1}}$. The effect of increasing hypoventilation on the relationship is also shown: A = $\dot V\mathrm{A}$ 3000 ml min^{-1}; B = $\dot V\mathrm{A}$ 2000 ml min^{-1}; C = $\dot V\mathrm{A}$ 1500 ml min^{-1}; D = $\dot V\mathrm{A}$ 1000 ml min^{-1}.

content difference of 50 ml litre^{-1}. We based our oxyhaemoglobin dissociation curve on the tables of Kelman and Nunn [6].

The $P\mathrm{I}_{\mathrm{O_2}}$ vs $Sa_{\mathrm{O_2}}$ *relationship*

The oxygen dissociation curve gives the relationship between arterial oxygen partial pressure ($Pa_{\mathrm{O_2}}$) and arterial oxyhaemoglobin saturation ($Sa_{\mathrm{O_2}}$). In an "ideal" lung in which all alveoli have a $\dot V/\dot Q$ ratio of 1 and without any shunt, diffusion defect or alveolar deadspace, the relationship between alveolar oxygen partial pressure ($P\mathrm{A}_{\mathrm{O_2}}$) and $Sa_{\mathrm{O_2}}$ corresponds exactly to the shape and position of the oxygen dissociation curve. If one then considers the position of the relationship between inspired oxygen partial pressure ($P\mathrm{I}_{\mathrm{O_2}}$) and $Sa_{\mathrm{O_2}}$, this curve would also correspond to the shape of the oxygen dissociation curve but would lie to the right by an amount corresponding to the $P\mathrm{I}_{\mathrm{O_2}}-P\mathrm{A}_{\mathrm{O_2}}$ gradient. The net result is the curve shown in figure 1; we refer to this curve as the "ideal" $P\mathrm{I}_{\mathrm{O_2}}$ *vs* $Sa_{\mathrm{O_2}}$ relationship.

Factors affecting the ideal $P\mathrm{I}_{\mathrm{O_2}}$ vs $Sa_{\mathrm{O_2}}$ *relationship*

The oxygen dissociation curve. Any factor which affects the position of this curve (pH, carbon dioxide, temperature, 2,3-diphosphoglycerate, carboxyhaemoglobin) will cause a corresponding change in the position and shape of the $P\mathrm{I}_{\mathrm{O_2}}$ *vs* $Sa_{\mathrm{O_2}}$ relationship [6].

As carbon dioxide and oxygen exchange are closely related, $Pa_{\mathrm{CO_2}}$ is altered by gas exchange impairment that causes hypoxaemia. This leads to Bohr effects causing a rightwards shift of the oxygen dissociation curve with increased $Pa_{\mathrm{CO_2}}$. In addition, blood from low $\dot V/\dot Q$ units will have a greater $Pa_{\mathrm{CO_2}}$ than blood from high $\dot V/\dot Q$ units. This produces a Bohr shift in the blood returning from low $\dot V/\dot Q$ units which is related to the magnitude of the gas exchange abnormality. The magnitude of the error introduced by not incorporating the effect of carbon dioxide exchange is very small (see Appendix 1).

The $P\mathrm{I}_{\mathrm{O_2}}-P\mathrm{A}_{\mathrm{O_2}}$ *gradient.* This is given by the alveolar gas equation in the form:

$$P\mathrm{I}_{\mathrm{O_2}}-P\mathrm{A}_{\mathrm{O_2}} = P\mathrm{B}_{\mathrm{dry}}\,\dot V\mathrm{O_2}/\dot V\mathrm{A} \qquad (1)$$

Using the assumed values for $P\mathrm{B}_{\mathrm{dry}}$ and $\dot V\mathrm{O_2}$, and with $\dot V\mathrm{A}$ 4000 ml:

$$P\mathrm{I}_{\mathrm{O_2}}-P\mathrm{A}_{\mathrm{O_2}} = 5.86\ \mathrm{kPa}$$

Any factor which increases this gradient causes a translocation of the curve to the right as an increased $P\mathrm{I}_{\mathrm{O_2}}$ is required to produce a given $P\mathrm{A}_{\mathrm{O_2}}$. Increased oxygen consumption or reduced alveolar ventilation produces this effect.

Hypoventilation. From equation (1) it can be seen that, for given $\dot V\mathrm{O_2}$, if $\dot V\mathrm{A}$ is reduced then $P\mathrm{I}_{\mathrm{O_2}}-P\mathrm{A}_{\mathrm{O_2}}$ is increased. For the whole lung, it can be seen that hypoventilation behaves as a reduction of the $\dot V/\dot Q$ ratio of all units and produces a displaced $P\mathrm{I}_{\mathrm{O_2}}$ *vs* $Sa_{\mathrm{O_2}}$ relationship. Figure 1 shows the ideal curve with a series of curves showing the shift produced by hypoventilation.

Abnormalities of gas exchange

The effect of true shunt and $\dot V/\dot Q$ distribution abnormality are analysed separately.

True shunt. Consider the effect of shunt in the absence of $\dot V/\dot Q$ distribution abnormality. In this situation, one may think in terms of a two-compartment model of true shunt and ideal alveoli. One may determine the effect of a shunt on the position of the $P\mathrm{A}_{\mathrm{O_2}}$ *vs* $Sa_{\mathrm{O_2}}$ relationship by calculating the resulting oxygen content when mixing end-capillary blood ($= P\mathrm{A}_{\mathrm{O_2}}$) with mixed venous blood in the proportion of the shunt at varying values of $P\mathrm{I}_{\mathrm{O_2}}$. The well known shunt equation is used:

$$\dot Q\mathrm{s}/\dot Q\mathrm{t} = (Cc'_{\mathrm{O_2}} - Ca_{\mathrm{O_2}})/(Cc'_{\mathrm{O_2}} - C\bar v_{\mathrm{O_2}}) \qquad (2)$$

Arterial to mixed venous oxygen content difference is assumed to be 50 ml litre^{-1} and this is incorporated into equation (2) by expressing it in the form:

$$Ca_{\mathrm{O_2}} = Cc'_{\mathrm{O_2}} - \dot Q\mathrm{s}/\dot Q\mathrm{t} \times (Ca_{\mathrm{O_2}} - C\bar v_{\mathrm{O_2}})/(1-\dot Q\mathrm{s}/\dot Q\mathrm{t}) \qquad (3)$$

Repeating this procedure with varying degrees of shunt results in a series of oxygen content lines each displaced from the ideal line (zero shunt) by a factor of $(Ca_{\mathrm{O_2}} - C\bar v_{\mathrm{O_2}})/(1-\dot Q\mathrm{s}/\dot Q\mathrm{t})$. Converting to oxyhaemoglobin saturation results in virtual shunt isopleths as shown in figure 2. These are plotted as $P\mathrm{I}_{\mathrm{O_2}}$ *vs* $Sa_{\mathrm{O_2}}$ and assume a $P\mathrm{I}_{\mathrm{O_2}}-P\mathrm{A}_{\mathrm{O_2}}$ gradient of 5.86 kPa.

$\dot V/\dot Q$ *mismatch.* Consider the effect of $\dot V/\dot Q$ mismatch in the absence of true shunt. The $\dot V/\dot Q$ ratios of alveoli in the lung are scattered and in theory could range from 0 to infinity. Estimations of the spread of $\dot V/\dot Q$ ratios in the lung using multiple inert gas elimination techniques [5] give results such as those illustrated in figure 3B [7]. This gives the blood flow and ventilation to units of differing $\dot V/\dot Q$ values; each point represents a different compartment (43 in total). In our model we have reduced the number of compartments to nine, each having a mean $\dot V/\dot Q$ of 0, 0.1, 0.3, 0.5, 1, 2, 4, 10 and infinity. The size of each compartment is dependent upon its blood supply and may be zero. When a particular distribution is applied to our model, the various points are assigned to the nearest compartment and

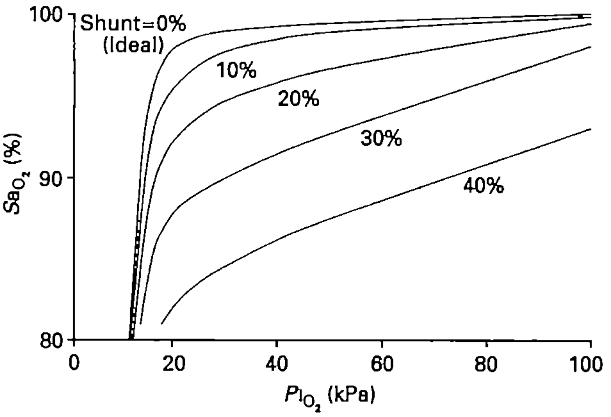

FIG. 2. Inspired oxygen partial pressure *vs* oxyhaemoglobin saturation, showing the calculated effect of different degrees of virtual shunt in accordance with the assumed model values given in the text. $P\text{I}_{O_2} - P\text{A}_{O_2} = 5.86$ kPa.

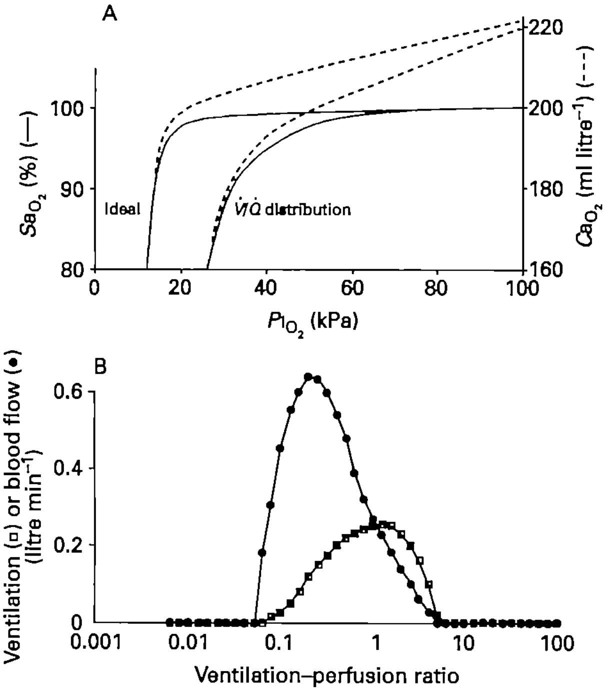

FIG. 3. A: Oxygen content (- - -) and oxyhaemoglobin saturation (——) *vs* $P\text{I}_{O_2}$ for an ideal lung and a lung with the $\dot{V}/\dot{Q}$ abnormality shown in figure 5B. B: Compartmental distribution of ventilation (□) and blood flow (●) with respect to ventilation–perfusion ratio. Results similar to this are obtained using the multiple inert gas elimination technique. (Redrawn from Dueck [7].)

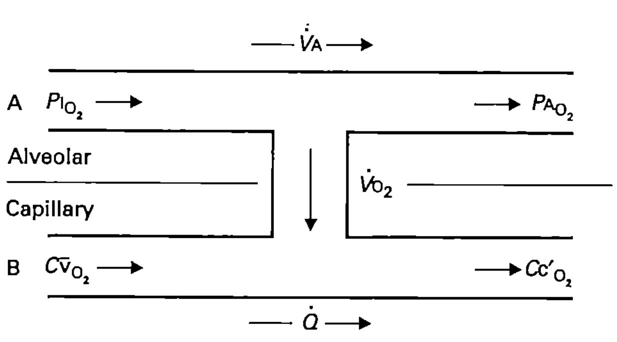

FIG. 4. Diagrammatic representation of alveolar ventilation and perfusion showing how each can be represented by a Fick equation (see text).

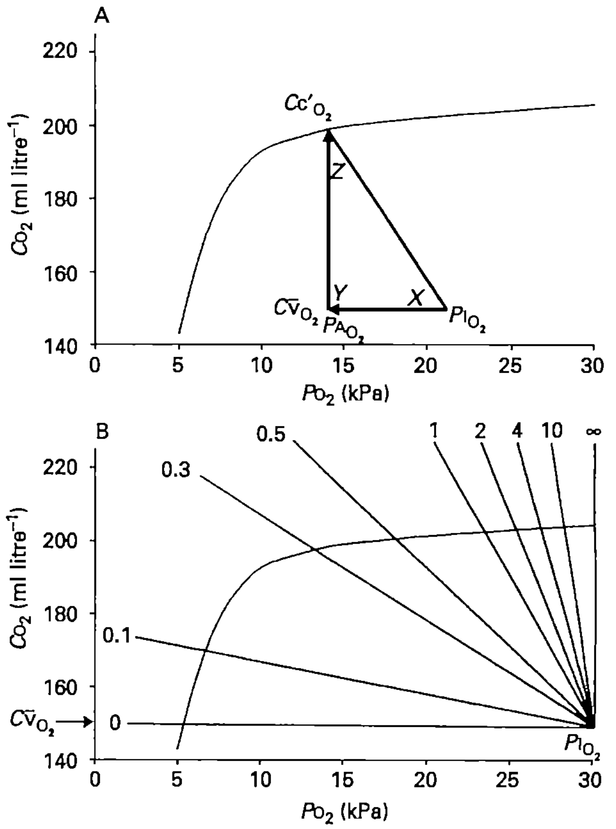

FIG. 5. A: Oxygen partial pressure *vs* oxygen content assuming a haemoglobin concentration of 15.27 g litre^{-1}. The graphical solution to equation (5) is shown. (See text for discussion.) B: For given $P\text{I}_{O_2}$ and $C\bar{v}_{O_2}$, a series of lines of differing gradient, representing the solution of equation (6) for varying $\dot{V}/\dot{Q}$, can be drawn. The intersection of these lines with the oxygen content curve give the end-capillary content of compartments of differing $\dot{V}/\dot{Q}$. Note that the horizontal line for zero $\dot{V}/\dot{Q}$ meets the ordinate at $C\bar{v}_{O_2}$. In this example the $\dot{V}/\dot{Q}$ lines are set for $P\text{I}_{O_2}$ 30 kPa and $C\bar{v}_{O_2}$ 150 ml litre^{-1}.

the total blood flow to each compartment is the sum of the blood flow to individual points. Appendix 2 demonstrates how this is applied to the data in figure 3B.

To ascertain the contribution of each compartment to the oxygen content of arterial blood, it is necessary to understand how the $P\text{I}_{O_2} - P\text{A}_{O_2}$ gradient at any given $\dot{V}/\dot{Q}$ alters with $P\text{I}_{O_2}$. The diagram in figure 4 describes the dynamics of oxygen uptake from an alveolus into a capillary. Using the Fick principle it can be seen that, for the alveolar component (A):

$$P\text{I}_{O_2} - P\text{A}_{O_2} = k\,\dot{V}O_2/\dot{V}\text{A} \qquad (4)$$

Similarly for the capillary component (B):

$$Cc'_{O_2} - C\bar{v}_{O_2} = \dot{V}O_2/\dot{Q} \qquad (5)$$

Combining these two equations in terms of $\dot{V}\text{A}/\dot{Q}$:

$$\dot{V}\text{A}/\dot{Q} = k(Cc'_{O_2} - C\bar{v}_{O_2})/(P\text{I}_{O_2} - P\text{A}_{O_2}) \qquad (6)$$

If $P\text{I}_{O_2}$ is known and $C\bar{v}_{O_2}$ is assumed, a graphical solution to this equation may be undertaken using the oxygen content curve as shown in figure 5A (see [8]). A triangle is formed by the points $x(P\text{I}_{O_2})$, $y(P\text{A}_{O_2}$ and $C\bar{v}_{O_2})$, and $z(Cc'_{O_2})$. The gradient of the hypotenuse of this triangle is given by $(Cc'_{O_2} - C\bar{v}_{O_2})/(P\text{I}_{O_2} - P\text{A}_{O_2})$ and from equation (6);

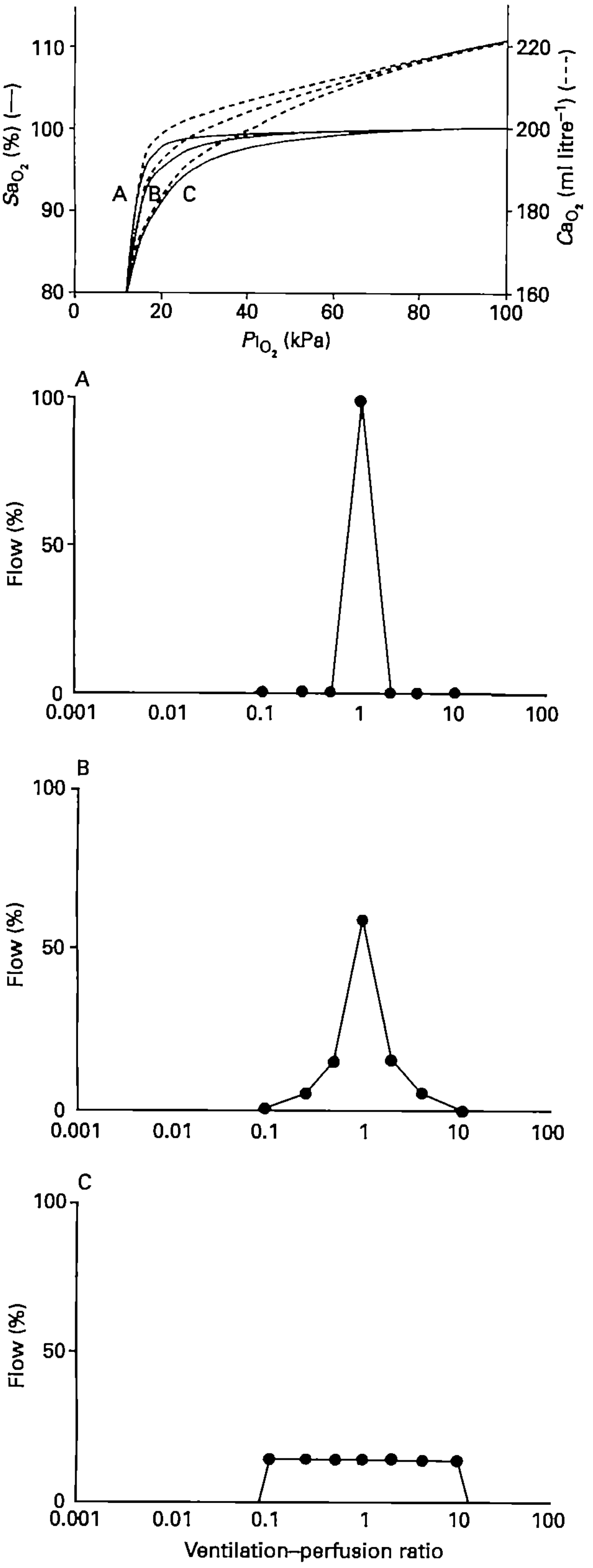

FIG. 6. Oxygen content (——) and oxyhaemoglobin saturation (——) *vs* $P\mathrm{I}_{\mathrm{O}_2}$ for an ideal lung (A) and two lungs (B and C) with increased spread of $\dot V/\dot Q$ about a mean of 1. The corresponding $\dot V/\dot Q$ distributions are shown below (A–C). In all examples shunt and deadspace = 0. Flow = blood flow (% of total).

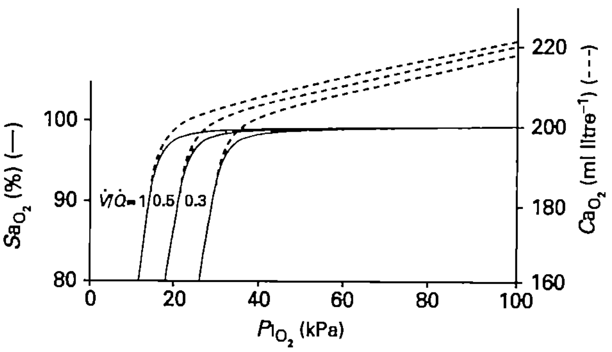

FIG. 7. Oxygen content (---) and oxyhaemoglobin saturation (——) *vs* $P\mathrm{I}_{\mathrm{O}_2}$ for an ideal lung ($\dot V/\dot Q = 1$), and two lungs with overall mean $\dot V/\dot Q$ ratios of 0.5 and 0.3.

this is therefore proportional to $\dot V/\dot Q$. When content is expressed in ml litre^{-1} and partial pressure in kPa, the coefficient of proportionality is 0.113 [8]. A series of these lines may be constructed of differing gradients representing differing $\dot V/\dot Q$ values. They can be placed over a content curve (using a transparent overlay) for any values of $P\mathrm{I}_{\mathrm{O}_2}$ and $C\bar{\mathrm{v}}_{\mathrm{O}_2}$ and the intercept of the line with the oxygen content curve gives Cc'_{O_2} for that $\dot V/\dot Q$ compartment. Figure 5B shows this for $P\mathrm{I}_{\mathrm{O}_2}$ 30 kPa and $C\bar{\mathrm{v}}_{\mathrm{O}_2}$ 150 ml litre^{-1}. This method was used to calculate the contribution of differing $\dot V/\dot Q$ compartments at differing $P\mathrm{I}_{\mathrm{O}_2}$ values. As the proportion of pulmonary blood flow to each compartment is known, from figure 5 the relative contributions of each compartment to the final Ca_{O_2} may be read and a weighted mean calculated; this is then converted to Sa_{O_2}. This process can be repeated at different values of $P\mathrm{I}_{\mathrm{O}_2}$ to construct a curve of $P\mathrm{I}_{\mathrm{O}_2}$ *vs* Sa_{O_2} in the presence of any given spread of $\dot V/\dot Q$ mismatch (see Appendix 2 for details of working).

The arterial-to-mixed venous oxygen extraction of 50 ml litre^{-1} must be held constant when the above graphical method is used. For each calculation, $C\bar{\mathrm{v}}_{\mathrm{O}_2}$ is estimated and the resulting Ca_{O_2} calculated. If the result is such that $Ca_{\mathrm{O}_2} - C\bar{\mathrm{v}}_{\mathrm{O}_2}$ is not equal to 50 ml litre^{-1}, $C\bar{\mathrm{v}}_{\mathrm{O}_2}$ is re-estimated and the process repeated. We accepted a tolerance of ± 2 ml litre^{-1}.

The effect of an abnormal $\dot V/\dot Q$ distribution can be considered in terms of the effect of mean $\dot V/\dot Q$ and the effect of $\dot V/\dot Q$ distribution. A lung with $\dot V/\dot Q = 1$, with little or no distribution about this value, gives an ideal $P\mathrm{I}_{\mathrm{O}_2}$ *vs* Sa_{O_2} curve. Modelling the effect of increasing $\log_{\mathrm{SD}} \dot Q$ with constant mean $\dot V/\dot Q = 1$ results in the curves shown in figure 6 (a flattening of the knee of the curve). Alterations in mean $\dot V/\dot Q$ to smaller values results in much larger movements of the curve to the right, as the effect is to increase the value of $P\mathrm{I}_{\mathrm{O}_2} - P\mathrm{A}_{\mathrm{O}_2}$. Figure 7 shows a series of curves of different mean $\dot V/\dot Q$ using the above model with 100% of the blood flow through that particular compartment. These simply show the magnitude of the shift which occurs with alterations in mean $\dot V/\dot Q$ alone. They are quite hypothetical, as $\dot V/\dot Q$ is never limited to one value, but occurs as a wide scatter. The combination of low $\dot V/\dot Q$ (shift) and scatter of $\dot V/\dot Q$ (flattening) is seen in figure 3 using data obtained from a patient [7].

Combined effect of $\dot V/\dot Q$ *mismatch and shunt.* The effect of shunt is easily modelled by adding the shunt component to the compartment of $\dot V/\dot Q = 0$ in the above model.

DISCUSSION

We have described the relationship between $P\text{I}_{O_2}$ and $S\text{a}_{O_2}$ and analysed the effect of various abnormalities of gas exchange on the shape and position of this relationship. The salient findings of the analysis are as follows.

(1) The $P\text{I}_{O_2}$ *vs* $S\text{a}_{O_2}$ curve reflects the shape of the oxygen dissociation curve, but lies to the right by the $P\text{I}_{O_2}-P\text{A}_{O_2}$ difference (fig. 1).

(2) Any factor which alters the position of the oxygen dissociation curve itself, or alters the value of $P\text{I}_{O_2}-P\text{A}_{O_2}$, alters the degree of this lateral movement also.

(3) The effect of true shunt considered alone is to produce the series of curves shown in figure 2, with a predominantly vertical depression of the plateau of the $P\text{I}_{O_2}$ *vs* $S\text{a}_{O_2}$ curve and relatively little lateral movement. The slope of the plateau which occurs on these shunt isopleths is caused by increasing oxygen content of non-shunted blood, derived from increased dissolved oxygen at greater values of $P\text{I}_{O_2}$.

(4) The effect of an increasing abnormal scatter of $\dot{V}/\dot{Q}$ ratios about a widening mean (increasing $\log_{SD}\dot{Q}$) is to produce a flattening of the knee of the curve (fig. 6).

(5) The effect of a reduced mean $\dot{V}/\dot{Q}$ ratio, as could be produced by changes in alveolar ventilation or cardiac output, is a marked rightwards lateral displacement of the relationship as a consequence of an increase in the $P\text{I}_{O_2}-P\text{A}_{O_2}$ difference (fig. 7).

(6) The combined effect of scatter of $\dot{V}/\dot{Q}$ ratios and reduced mean $\dot{V}/\dot{Q}$ is to produce a laterally displaced curve with flattening (fig. 8).

Riley and Cournand, in 1949 [2], described a three-compartment model of the lung involving shunt, ideal alveoli and deadspace. Using this model in its original form, the Dueck data (fig. 3B) would be resolved into a compartment of shunt and a compartment of ideal alveoli. This could then be incorporated into the multicompartmental model described in this paper by setting the size of all compartments to zero except $\dot{V}/\dot{Q} = 0$ (shunt) and $\dot{V}/\dot{Q} = 1$ (ideal alveoli). The resultant $P\text{I}_{O_2}$ *vs* $S\text{a}_{O_2}$ curve would show a shunt effect, but would have no shift and no flattening. Modifying the model to include shunt, low $\dot{V}/\dot{Q}$ and high $\dot{V}/\dot{Q}$ compartments would improve the resolution, but the shape of the $P\text{I}_{O_2}$ *vs* $S\text{a}_{O_2}$ curve would be dependent upon the position and size of these $\dot{V}/\dot{Q}$ compartments. Multiple inert gas determination of $\dot{V}/\dot{Q}$ distribution used a large number of compartments in order to describe the position and size of these distributions. Any number of compartments can be chosen to model the spread of $\dot{V}/\dot{Q}$ ratios, but we chose seven in addition to shunt ($\dot{V}/\dot{Q} = 0$) and deadspace ($\dot{V}/\dot{Q} = \text{infinity}$), as these enabled a reasonable sample of $\dot{V}/\dot{Q}$ ratios to be distinguished over the range in which published $\dot{V}/\dot{Q}$ ratios tend to occur over a log scale. They enable the position and spread of the $\dot{V}/\dot{Q}$ distribution to be modelled with sufficient accuracy to demonstrate the effects that these abnormalities have on the $P\text{I}_{O_2}$ *vs* $S\text{a}_{O_2}$ curve. An infinite number of compartments would be required ideally to produce an accurate model of scatter. With fewer than nine compartments, the important effect of wide $\dot{V}/\dot{Q}$ scatter is progressively lost and, with more, little is gained in this respect but the model becomes increasingly cumbersome. Using the three-compartment model of Riley and Cournand [2], the flattening effect of an increased spread of $\dot{V}/\dot{Q}$ ratios would not be seen at all.

The use of the multiple inert gas technique for estimation of $\dot{V}/\dot{Q}$ results in a narrow peaked distribution in young healthy volunteers [9]. Widening of the $\dot{V}/\dot{Q}$ distribution (greater $\log_{SD}\dot{Q}$) has been reported in middle-aged subjects under anaesthesia [10]. Much larger widening has been reported in aged patients with pulmonary disease [7]. A wide $\dot{V}/\dot{Q}$ distribution redrawn from the latter study is shown in figure 3B.

Figure 6 shows how increasing $\dot{V}/\dot{Q}$ mismatch (increased $\log_{SD}\dot{Q}$) affects the relationship with a flattening of the knee of the curve, even without alterations in mean $\dot{V}/\dot{Q}$.

The effect of abnormal $\dot{V}/\dot{Q}$ distributions on oxygen content as derived from the graphical model described above is shown in figure 6. Note how the difference in content between blood from an ideal lung and blood from a lung with a $\dot{V}/\dot{Q}$ abnormality is small at large values of $P\text{I}_{O_2}$ and becomes increasingly large at smaller $P\text{I}_{O_2}$ values. This is in contrast with the content difference of blood from an ideal lung and blood from a lung with true shunt, which remains constant at varying $P\text{I}_{O_2}$ values. The increased content difference at small $P\text{I}_{O_2}$ with a $\dot{V}/\dot{Q}$ abnormality occurs because, as $P\text{I}_{O_2}$ is reduced, content in units of low $\dot{V}/\dot{Q}$ begins to occur on the steep part of the content curve, hence reducing $C\text{a}_{O_2}$. The corresponding $P\text{I}_{O_2}$ *vs* $S\text{a}_{O_2}$ curves are shown also and illustrate the flattening displacement which occurs with this abnormality.

A reduction in mean $\dot{V}/\dot{Q}$ results in a rightwards displacement. This may be seen from equation (6) in which, for a constant ($P\text{a}_{O_2}-P\bar{\text{v}}_{O_2}$), a decrease in $\dot{V}/\dot{Q}$ will involve an increased $P\text{I}_{O_2}-P\text{A}_{O_2}$ difference. This assumption of constant ($P\text{a}_{O_2}-P\bar{\text{v}}_{O_2}$) implies that these are "virtual" shunt and $\dot{V}/\dot{Q}$ model lines.

With small values of $P\text{I}_{O_2}$ there are confounding effects not otherwise taken into account in the model described. An abnormal $\dot{V}/\dot{Q}$ scatter which causes an impairment of oxygenation also causes an impairment of carbon dioxide transfer and an increase in $P\text{a}_{CO_2}$ occurs. This would tend to exacerbate a rightwards shift as increased $P\text{a}_{CO_2}$ causes a shift of the oxygen dissociation curve to the right by the Bohr effect. A gas exchange abnormality of the magnitude of that shown in figure 3B would result in a $P\text{a}_{CO_2}$ of 5.47 kPa if $\dot{V}\text{A}$ remained constant. The Bohr shift occasioned by this would cause a further rightwards shift of approximately 0.06 kPa. However, this effect will be offset "*in vivo*" by an increase in $\dot{V}\text{A}$ causing an increase in $\dot{V}\text{A}/\dot{Q}$ and decrease in $P\text{a}_{CO_2}$.

When $F\text{I}_{O_2}$ is altered clinically, many other factors also influence the effect of a given $\dot{V}/\dot{Q}$ abnormality. Cardiac output would be unlikely to remain constant at progressive degrees of hypoxaemia and an increase would decrease the overall $\dot{V}/\dot{Q}$, causing a leftwards shift. Hypoxaemia is also often accompanied by progressive hyperventilation, which also alters overall $\dot{V}/\dot{Q}$ and causes an increasing rightwards shift. All of these factors could change at different $P\mathrm{I}_{\mathrm{O}_2}$ during the construction of a $P\mathrm{I}_{\mathrm{O}_2}$ *vs* $S\mathrm{a}_{\mathrm{O}_2}$ curve, in which case the *in vivo* curves would deviate from the model curve. This does not invalidate the model, as a new curve can be constructed for any given value of pH, carbon dioxide, cardiac output and alveolar ventilation. What occurs is that the patient's $S\mathrm{a}_{\mathrm{O}_2}$ moves from one model curve to another as various factors assumed constant for the construction of the original curve are changed.

It can be seen that the exact position of the steep part of the curve is altered by many factors which alter in the perioperative period. Alterations in overall $\dot{V}/\dot{Q}$ probably are the most important factors, as they can bring the steep part of the curve into the clinical range (fig. 7).

In figures 2, 3, 6 and 7, $P\mathrm{I}_{\mathrm{O}_2}$ is shown on the x axis at values up to 100 kPa. This is to make clear the mathematical working of the model and to show how shunt and $\dot{V}/\dot{Q}$ differ in their effects at increased $P\mathrm{I}_{\mathrm{O}_2}$. In practice, however, there will be confounding factors at increased $P\mathrm{I}_{\mathrm{O}_2}$. Absorption atelectasis and reversal of hypoxic pulmonary vasoconstriction are both likely to alter the position of these curves at $P\mathrm{I}_{\mathrm{O}_2}$ values > 80 kPa.

The widespread adoption of pulse oximetry has made the measurement of oxygen saturation simple and non-invasive. Knowledge of the $P\mathrm{I}_{\mathrm{O}_2}$ *vs* $S\mathrm{a}_{\mathrm{O}_2}$ relationship and the mechanisms underlying changes therein are important in interpreting the significance of single $S\mathrm{a}_{\mathrm{O}_2}$ values. Before pulse oximetry was available, it was commonplace to judge oxygen requirements by measuring $P\mathrm{a}_{\mathrm{O}_2}$ at a known $P\mathrm{I}_{\mathrm{O}_2}$ and reading the degree of shunt from a series of isopleths [11]. This could be done similarly using shunt isopleths expressed in terms of saturation (fig. 2). However, our earlier data [1, 12] showed a marked deviation from these isopleths at smaller values of $P\mathrm{I}_{\mathrm{O}_2}$. It had been suggested previously that the degree of shunt attributable to a given distribution of $\dot{V}/\dot{Q}$ increases as $P\mathrm{I}_{\mathrm{O}_2}$ is reduced [3, 4]; this was confirmed by our model and was manifest in the $P\mathrm{I}_{\mathrm{O}_2}$ *vs* $S\mathrm{a}_{\mathrm{O}_2}$ curves as a lateral displacement and flattening of the steep part of the curve. This is of clinical significance as the steep part of the curve may move into the clinical range. In the study by Lawler and Nunn [13], some patients showed increased measured virtual shunt at smaller $P\mathrm{I}_{\mathrm{O}_2}$. This could be explained by the effect of a $\dot{V}/\dot{Q}$ abnormality at smaller values of $P\mathrm{I}_{\mathrm{O}_2}$. $P\mathrm{I}_{\mathrm{O}_2}$ *vs* $S\mathrm{a}_{\mathrm{O}_2}$ diagrams are sensitive to the difference in behaviour of true shunt and $\dot{V}/\dot{Q}$ maldistribution at varying $P\mathrm{I}_{\mathrm{O}_2}$.

We have not attempted to quantify plateau depression and shift in this paper. Any attempt to do so using curves obtained from patient data must take into account the interactions of the various patterns seen. Shunt (plateau depression) is best revealed as the depression in $S\mathrm{a}_{\mathrm{O}_2}$ at $P\mathrm{I}_{\mathrm{O}_2}$ 50 kPa, as here the effects of small mean $\dot{V}/\dot{Q}$ (shift) and a large $\log_{\mathrm{SD}} \dot{Q}$ (flattening) are minimized (figs 6, 7). The effect of $\dot{V}/\dot{Q}$ abnormalities (mean $\dot{V}/\dot{Q}$ and $\log_{\mathrm{SD}} \dot{Q}$) are absent at $P\mathrm{I}_{\mathrm{O}_2}$ 100 kPa, but here the effect of shunts less than 30% are harder to ascertain from saturation readings. Low mean $\dot{V}/\dot{Q}$ (shift) is best revealed at $S\mathrm{a}_{\mathrm{O}_2}$ 80%, as here the effect of shunt and large $\log_{\mathrm{SD}} \dot{Q}$ are also minimized (figs 2, 6). This would be difficult to achieve clinically in most patients without the administration of subatmospheric partial pressures of oxygen. However, an indication of the low $\dot{V}/\dot{Q}$ effect (shift) may be obtained by plotting a series of $S\mathrm{a}_{\mathrm{O}_2}$ values over a wide range and detecting deviation from the shunt isopleth with smaller $P\mathrm{I}_{\mathrm{O}_2}$.

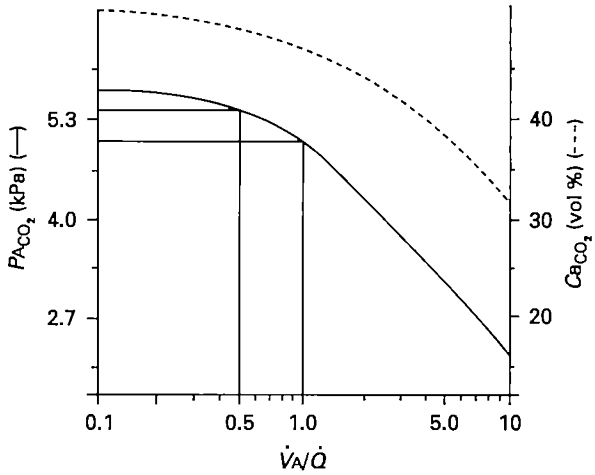

FIG. 8. $\dot{V}/\dot{Q}$ *vs* $P\mathrm{A}_{\mathrm{CO}_2}$ and $C\mathrm{a}_{\mathrm{CO}_2}$ showing the effect on $P\mathrm{A}_{\mathrm{CO}_2}$ of a reduction in $\dot{V}/\dot{Q}$ from 1 to 0.5. (See Appendix 1 for discussion.) (Reproduced from Fahri [8].)

In conclusion, measurement of the $P\mathrm{I}_{\mathrm{O}_2}$ *vs* $S\mathrm{a}_{\mathrm{O}_2}$ relationship is a simple, non-invasive extension of the use of pulse oximetry. It gives useful information regarding both the aetiology of hypoxaemia and the likely behaviour of oxygen saturation in the perioperative period. Reference to the oxygen dissociation curve alone when interpreting oxygen saturation results can be very misleading, as the position of the $P\mathrm{I}_{\mathrm{O}_2}$ *vs* $S\mathrm{a}_{\mathrm{O}_2}$ relationship may alter widely in the perioperative period.

APPENDIX 1

Carbon dioxide exchange is related to $\dot{V}/\dot{Q}$ by the following equation, which is derived using the same principles as equation (6):

$$\dot{V}\mathrm{A}/\dot{Q} = k(C\bar{\mathrm{v}}_{\mathrm{CO}_2} - C\mathrm{a}_{\mathrm{CO}_2})/P\mathrm{A}_{\mathrm{CO}_2} \qquad (7)$$

The solution to this equation is also by the graphical method, but using the carbon dioxide dissociation curve. Figure 8 (reproduced from Fahri [8]) shows how $P\mathrm{A}_{\mathrm{CO}_2}$ and $C\mathrm{a}_{\mathrm{CO}_2}$ vary with $\dot{V}/\dot{Q}$. Table I shows the effect of reducing $\dot{V}/\dot{Q}$ from 1 to 0.5 on $P\mathrm{a}_{\mathrm{CO}_2}$ (assuming [8] that $P\mathrm{A}_{\mathrm{CO}_2} = P\mathrm{a}_{\mathrm{CO}_2}$ at low $\dot{V}/\dot{Q}$). The effect on pH, derived using a Siggaard–Andersen nomogram is shown, and the effect that the consequent Bohr shift will have on a $P\mathrm{a}_{\mathrm{O}_2}$ of 6 kPa (chosen as this is on the steep part of the oxyhaemoglobin dissociation curve).

TABLE I. *Effect of* $\dot{\mathrm{V}}/\dot{\mathrm{Q}}$ *on* Pa_{CO_2}, *pH and* Pa_{O_2}

	$\dot{V}/\dot{Q}$	
	1	0.5
$P\mathrm{a}_{\mathrm{CO}_2}$ (kPa)	5.07	5.47
pH	7.40	7.39
$P\mathrm{a}_{\mathrm{O}_2}$ (kPa)	6	5.94

APPENDIX 2

ILLUSTRATION OF THE WORKING OF THE MODEL

The Dueck data (fig. 3B) have been rationalized into the following compartments (table II).

TABLE II

	$\dot{V}/\dot{Q}$								
	0	0.1	0.3	0.5	1	2	4	10	∞
Blood flow (%)	0	22	36	21	12	6	2	0	0

To estimate Sa_{O_2} at PI_{O_2} 25 kPa

Mixed venous oxygen content is estimated at 110 ml litre^{-1}.

Using the transparency of figure 5B over the oxygen content curve: for a mixed venous oxygen content 110 ml litre^{-1} the line of $\dot{V}/\dot{Q} = 0$ on the transparency is set at 110 on the ordinate and for PI_{O_2} 25 kPa the line of $\dot{V}/\dot{Q}$ = infinity on the transparency is set at 25 on the abscissa. The intersection of the $\dot{V}/\dot{Q}$ lines on the transparency with the oxygen content curve gives the end-capillary oxygen content of blood leaving each compartment (table III).

TABLE III

	$\dot{V}/\dot{Q}$								
	0	0.1	0.3	0.5	1	2	4	10	∞
Cc'_{O_2} (ml litre^{-1})	—	125	158	180	196	198	200	—	—

A weighted mean of these Cc'_{O_2} values is calculated using the percentage of the total blood flow to each compartment as the weighting. For the above data this is 161.6 ml litre^{-1}, giving an oxygen saturation of 80.4%. Note how this gives an arterial-to-mixed venous oxygen content difference of 51.6 ml litre^{-1} which is acceptable, as our tolerance is 48–52 ml litre^{-1}. If it had been outside this range, $C\bar{v}_{O_2}$ would have to be re-estimated and the above working repeated. The above process is repeated over a wide range of PI_{O_2} values to construct a curve of PI_{O_2} *vs* Sa_{O_2}.

The relationship between Ca_{O_2} and Sa_{O_2} may be inferred from a graph constructed using the oxyhaemoglobin dissociation curve with an allowance for dissolved oxygen.

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British Journal of Anaesthesia 1993; 71: 495–498

STUDY OF THE ANATOMY OF THE EXTRADURAL REGION USING MAGNETIC RESONANCE IMAGING

J. L. WESTBROOK, S. A. RENOWDEN AND L. E. S. CARRIE

SUMMARY

We have studied magnetic resonance images of the lumbar spine of 39 subjects to examine the anatomy of the lumbar extradural region. The segmental nature of the posterior extradural region at each lumbar level may explain reports of easier cranial passage of extradural catheters introduced by the paramedian approach. This approach may thus provide a more reliable route for rapid introduction of an extradural catheter during the needle-through-needle, combined spinal–extradural technique. (Br. J. Anaesth. 1993; **71**: 495–498)

KEY WORDS

Anatomy: extradural space. Anaesthetic techniques: extradural. Measurement techniques: magnetic resonance imaging.

Most anaesthetic texts describing the conduct of extradural anaesthesia stress the importance of a detailed knowledge of the anatomy of the region. Unfortunately, descriptions in standard anatomy or anaesthetic books may not provide the reader with a clear or accurate image of the anatomy or dimensions of this area, the most likely reason being the problems inherent in its study. The principal difficulty is that, in life, the extradural region exists largely as a "potential space" [1]—a term used by Bromage to reflect, not only the minimal contents of the extradural space but also its capacity to expand to accommodate very large volumes of injected fluid or air. Parkin and Harrison [2] have advocated use of the term "extradural region" rather than "extradural space" in order not to suggest a space of large resting volume.

Many different techniques have been used in the study of the anatomy of the extradural region, but they all have limitations and are subject to artefact. Cadaveric dissection [2] is subject to distortion because of postmortem autolysis and preservation with agents that alter tissue properties; furthermore, the loss of cerebrospinal fluid (CSF) pressure at death and possible increase in venous pressure result in changes in the relative volumes occupied by the dural sac and venous plexuses within the spinal canal. All techniques requiring the injection of fluid or air into the extradural region distort the anatomy; such methods have included resin injection studies [3], extradurography and computed tomography (CT) extradurography [4], extraduroscopy [5] and spinaloscopy [6]. More recently, a study using cryomicrotome sectioning of cadavers has provided some detailed information less distorted by artefact [7].

Magnetic resonance imaging (MRI) is the most rapidly advancing of the imaging specialties. Developments in computer technology have provided for greater image resolution, detailed tissue contrast without use of contrast media and images acquired in any plane. The physics of MRI has been reviewed [8].

The purpose of this study was to examine the anatomy and dimensions of the extradural region using MRI and to compare the information obtained with that from other investigative techniques.

PATIENTS AND METHODS

The anatomy of the lumbar extradural space was studied retrospectively using lumbar MRI scans of 39 patients. The examinations had been undertaken because of low back pain, but the images were reported as normal by a neuroradiologist.

The patients comprised 22 men and 17 women, aged 18–64 yr (median 38 yr). All MRI examinations were performed with a GE Signa Advantage scanner operating at 1.5 T (tesla), with the patient supine. Using a surface coil and fast spin echo (FSE), T1-weighted (T1W) and T2-weighted (T2W) sagittal scans were obtained, followed by FSE axial T2W scans through the lower four lumbar discs.

Using computer software, direct measurements were taken from the stored, computerized images in multiple planes at the L2–3 level (fig. 1) to record the following data: distance from the skin to the extradural region; the angle of the lumbar spinous processes relative to the long axis of the spine; distance between adjacent laminae; distance between the anterior surface of the ligamentum flavum and the dura at the cranial end of the lumbar segment, at the mid-point of the ligamentum flavum and at the

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Correspondence to L.E.S.C.

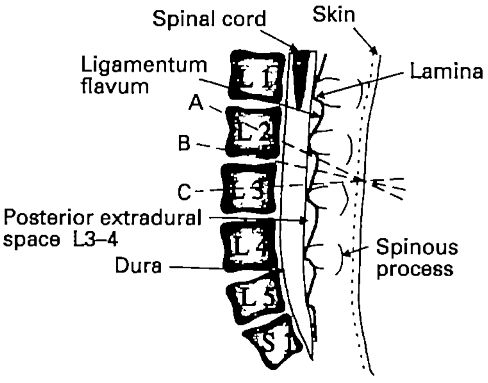

FIG. 1. Diagram showing anatomy and planes of measurement.

caudal end of the lumbar segment. These measurements were taken in a straight line from a "skin puncture" site between two adjacent spinous processes, as this would be the route followed by an extradural needle.

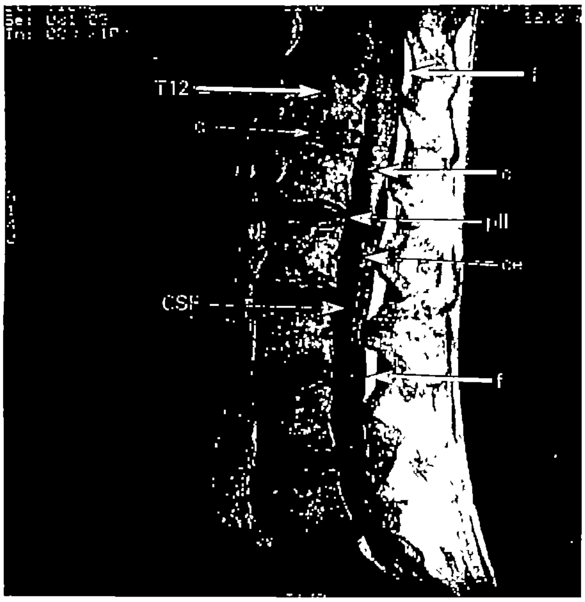

FIG. 2. T1W sagittal mid-line MR image showing vertebrae T11–S2, the intervening discs (d) and the overlying posterior longitudinal ligament (pll). The dural sac lies within the spinal canal. The CSF is of low signal (dark) and the conus (c), of higher signal, is located at L1. The nerve roots of the cauda equina (ce) are demonstrated to lie posteriorly. Posterior to the dural sac, extradural fat (f), which is of high signal (white) on T1W images, is demonstrated at levels T11–12 to L3–4, giving a "saw toothed" pattern to the extradural region. The fat is divided into segments by the interposing laminae. The extradural space is deeper at the cranial end than at the caudal end.

TABLE I. *Measurements taken from MR images at the L2–3 level (mean (SD) [range])*

Skin–ligamentum flavum	49.7 (11.75) [30–85] mm
Ligamentum flavum–dura mater	
Cranial	5.97 (1.35) [4–9] mm
Mid-point	6.15 (1.31) [4–9] mm
Caudal	3.95 (1.1) [2–7] mm
Interlaminar distance	21.44 (2.79) [15–27] mm
Angle of spinous process to long axis	70.7 (5.1) [63–83]°

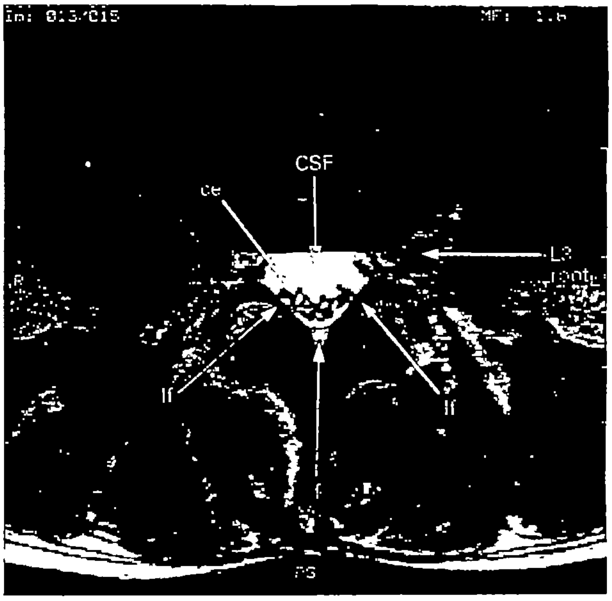

FIG. 3. T2W axial MR image at L3–4, between the two laminae. On T2W sequences CSF is of high signal (white) and the nerve roots of the cauda equina (ce) are well demonstrated within the dural sac. Fat is of intermediate signal; posterior to the dura is a triangle of extradural fat (f), bordered posterolaterally by the ligamentum flavum (lf). Laterally the confines of the extradural space are less defined.

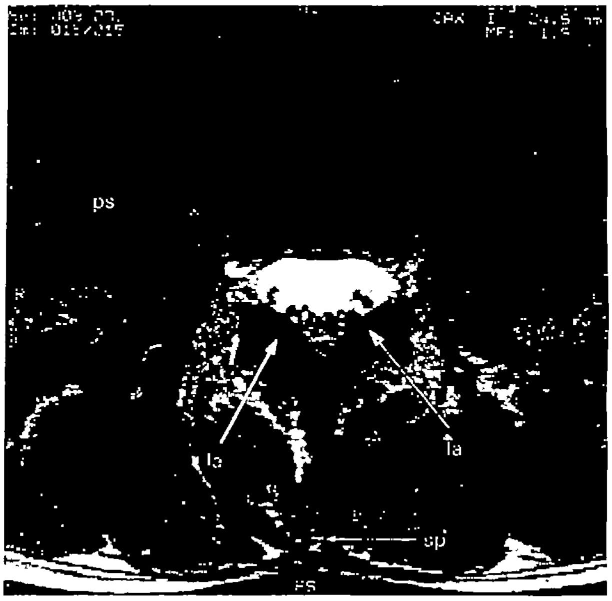

FIG. 4. T2W axial image at the level of the L3 lamina. The dural sac is located adjacent to the anterior surface of the lamina (la). There is no intervening extradural fat. sp = Spinous process of L3; ps = psoas muscle.

RESULTS

Representative MRI images are illustrated in figures 2–4. Measurements obtained at the L2–3 level are documented in table I. There was no significant difference between the results of male and female subjects.

DISCUSSION

The extradural region is contained entirely within the spinal canal and itself contains the spinal extension of the dural sac (terminating at S1–2 in the adult), nerve bundles, blood vessels, lymphatics and fat. Its superior margin is at the foramen magnum where the periosteum and dura fuse. The inferior margin of the extradural region is at the sacrococcygeal membrane. Anteriorly, the region is bounded by the posterior surface of the posterior longitudinal ligament overlying the vertebral bodies and intervertebral discs. The posterior margin of the extradural region comprises alternating vertebral laminae and the ligamentum flava on each side of the midline. Laterally the borders of the "space" are less well defined—the bony pedicles form part of the boundary and between them the intervertebral foramina; however, the exact point at which the extradural region ends and the paravertebral region begins within the foramina is not clearly defined.

The ligamentum flavum has been studied extensively. At each spinal level there are two ligamenta, one on each side of the midline, meeting at an angle of 90° or less [7, 9]. Most reports show that the ligamenta do not always meet in the mid-line, the gap being filled by the anterior margin of the interspinous ligament [2, 7, 9]. Cadaveric studies have shown the ligamentum flavum to be 2–5 mm thick [2, 9], although some authors have claimed the ligament to be up to 10 mm thick in obstetric patients [10, 11].

The feature of the extradural region that is very clearly demonstrated on mid-line sagittal sections on MRI is the segmented shape of the posterior extradural space. This has been shown previously using plain lumbar x-rays and CT after injection of iodized oil into the extradural space of 19 subjects [4]. The authors of that study described the shape of the extradural space in this plane as "saw-toothed". They recorded the depth of the extradural space at the cephalic end as 1.6 mm ± 0.32 mm and that at the caudal end 8.3 mm ± 1.95 mm (at the level of T12). This differs from the data obtained in the present study, in which the caudal end has been shown to be the narrower part of the space (3.95 mm) compared with the cranial end (5.97 mm). The former study required injection of contrast, which may have caused distortion; furthermore, the lower thoracic region was studied and compensation was not made for the magnification inherent in plain film images. These data have been quoted as a reason for attempting to enter the extradural space at its caudal end [12]. We agree with this recommendation, but for the different reason given below.

The segmentation of the posterior extradural region observed by us has been described previously in dissection studies. Parkin and Harrison [2] studied 12 embalmed cadavers, whilst Hogan [7] studied 38 cadavers using cryomicrotome techniques. The latter work is in agreement with the present study showing the segmental extradural region to be narrower at the caudal end.

It may be seen from the MR images in this study that, at each segmental level, the extradural region narrows abruptly at its cranial end as the lamina becomes adjacent to the dura. Should the Tuohy needle enter the space in this superior part, attempts at introducing the catheter may meet with almost immediate obstruction as it strikes the inferior surface of the laminae. This may be compared with a needle that enters the space at the caudal end and has unobstructed passage for the catheter of 15–27 mm. With the "blind" nature of the mid-line approach to the extradural space, the operator has little control over which portion of the ligamentum flavum is punctured. This study has shown that the angle of the spinous processes between which the mid-line needle must pass ranges from 63° to 83°. With the mid-line approach, if the spines are angled at 80°, the needle is likely to puncture the ligamentum flavum at its cephalic end. If the spines are at 60°, the needle is more likely to puncture the ligamentum flavum at the caudal end. Any such differences would be exaggerated, the greater the distance between the skin and the ligamentum flavum. However, the bony landmark afforded by the paramedian approach enables the operator to "walk off" the inferior lamina and so always enter the extradural space at the caudal end. This may explain reports showing that the passage of paramedian catheters is less commonly obstructed and that they more commonly follow a straight cranial path [5, 13–15].

Although entering the extradural space at its caudal and therefore shallower extent could be associated with a greater risk of dural puncture, the oblique passage of the extradural needle during the paramedian technique presents the dura with the rounded aspect of the Huber tip, thus making dural puncture unlikely. In addition, this angle of approach results in a catheter emerging from the needle in a plane more parallel to the dura and so less likely to cause tenting. It has been shown by Hardy [16] that a catheter cannot be pushed through intact dura, although it has been suggested that the dura may be punctured if already damaged by the Tuohy needle. Blomberg's extraduroscope study [5] of 14 cadavers confirms the above description, with all 14 paramedian catheters having a free cranial passage whilst all 14 mid-line catheters caused tenting of the dura and followed an unpredictable course.

A further controversy in the anatomy of this region is the possible presence of a dural fold extending posteriorly to the ligamentum flavum in the mid-line. This has been termed the plica mediana dorsalis [17] and should not be confused with the fibrous bands extending posteriorly in the mid-line between the dura and the ligamentum flavum. Such bands may be strong enough to divert extradural catheters [18]. One report using CT extradurography in 40 subjects described the plica mediana dorsalis as being present in 38; however, the authors were using the term to describe the fibrous bands and not true folds of dura [19]. As with other studies that did not involve the injection of fluid into the extradural region [2, 7] this study showed no evidence of a true plica mediana dorsalis. It would seem likely that previous descriptions have been the result of partial collapse of the dural sac by injected contrast or polyester resin [20] or on opening the extradural space at surgery. Under these circumstances, the fibrous bands support the mid portion of the dura, giving the impression of a fold [21].

Advantages of the paramedian approach to the extradural region have been argued by a number of authorities [5, 22, 23], yet the mid-line approach appears to remain that practised most commonly by anaesthetists. A recent survey of U.K. obstetric units showed that 85 % of anaesthetists preferred the mid-line approach, whilst 2 % only used the paramedian route [24]. Some have avoided the paramedian approach on the grounds that it is more painful. This observation was made in a comparative study with the mid-line approach [25] using the same concentration and volume of local anaesthetic for both techniques. In fact, the soft tissues traversed with the paramedian route allow for easy injection of larger volumes of local anaesthetic which should render the method virtually painless.

The images and dimensions obtained in this study lend further support to the use of the paramedian route for extradural anaesthesia. The clear bony landmarks afford the practitioner a known level for entering the extradural space, relative to the lamina, that is most likely to afford unobstructed passage of the extradural catheter. The increasing popularity of the combined spinal–extradural technique for regional anaesthesia in obstetrics may make this information more important. The needle-through-needle technique requires the easy passage of the extradural catheter after the injection of the subarachnoid local anaesthetic; this may be achieved more reliably by the paramedian route.

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British Journal of Anaesthesia 1993; 71: 499–502

SINGLE SPACE COMBINED SPINAL–EXTRADURAL TECHNIQUE FOR ANALGESIA IN LABOUR

R. G. W. STACEY, S. WATT, M. Y. KADIM AND B. M. MORGAN

SUMMARY

We have used the single space combined spinal–extradural technique for mothers requesting analgesia in labour. Intrathecal plain bupivacaine 5 mg produced a median time to analgesia of 3 min. There was inadequate abdominal analgesia after 10 min in 16% of recipients, although all had good perineal analgesia. The median height of block was T8 (range T4–L2) and mean duration of analgesia 72 (SD 21) min. Hypotension occurred in two of 30 mothers, but responded to fluids and ephedrine. There were no post-spinal headaches. This technique is suitable for those parturients requesting analgesia in active labour who may not have time to achieve extradural analgesia before delivery. The extradural catheter is used to improve analgesia if the subarachnoid block is inadequate, or if labour continues beyond the duration of the subarachnoid block. (Br. J. Anaesth. 1993; **71**: 499–502)

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: regional, spinal, extradural.

It is difficult to predict how fast the first stage of labour may progress in an individual multiparous woman. This, and occasional late requests for extradural analgesia, sometimes result in the insertion of extradural blocks too late for them to become fully established before delivery.

Injecting the local anaesthetic intrathecally is a means of achieving almost instantaneous analgesia at any stage of labour [1]. When used to provide analgesia for delivery, it has been associated with post lumbar puncture (PLP) headache in 16–20% of recipients [2, 3]. The incidence of PLP headache using a single space combined spinal–extradural (CSE) with 26-gauge needles in the obstetric population is 1–2% [4, 5]. The evolution of this technique has been well described [4, 6–9] and is used routinely at our hospital to provide anaesthesia for Caesarean section. For some years we have used a CSE technique with a small intrathecal dose of 0.25% bupivacaine to provide analgesia for multiparous women, or primiparous women with the urge to push against an undilated cervix.

We present an audit of data collected prospectively on the first 30 recipients of the technique in 1992. The anaesthetists performing the blocks were junior staff, with varying degrees of experience. None had used this single space CSE before.

PATIENTS AND METHODS

Women were informed of the technique by the anaesthetist before insertion of the block. Verbal consent to a spinal anaesthetic was obtained from 30 women who had had an uneventful pregnancy and were beyond 36 weeks gestation, with no contraindication to regional analgesia.

The procedure was undertaken with the mother in the left lateral position during preload of the circulation with crystalloid solution 1 litre. Using a midline approach at the L2–3 interspace, a 16-gauge Tuohy needle was introduced into the extradural space with the bevel facing cephalad. A Becton Dickinson 27-gauge, 12-cm needle with a Quincke type point was passed through the Tuohy needle with the bevel parallel to the dural fibres [10], until about 1 cm of the spinal needle projected beyond the Tuohy needle.

With the spinal needle positioned correctly, 15 s was allowed for outflow of cerebrospinal fluid (CSF) after which time, if no fluid was visible, an attempt to aspirate CSF was made. On the appearance of CSF, 0.25% plain bupivacaine 2 ml was injected over 10 s and the time noted.

On removal of the spinal needle, the extradural catheter was inserted without turning the needle, so that 3 cm remained in the extradural space.

The time taken to achieve adequate analgesia was judged as the time after the subarachnoid injection until the first painless contraction. The anaesthetist performing the block assessed the dermatomal level, at 5-min intervals for the first 30 min, as the loss of cold discrimination to ethyl chloride. Sympathetic block was recorded as the presence or absence of warm dry feet. A modified Bromage scale was used to assess motor block: 0 = able to lift legs against gravity; 1 = able to flex knee but unable to lift legs; 2 = able to move feet but unable to flex knee; 3 = no movement at all.

Arterial pressure was measured every 5 min for the first 30 min using a mercury column sphygmomanometer. Hypotension, recorded as systolic pressure less than 100 mm Hg or a 20% reduction

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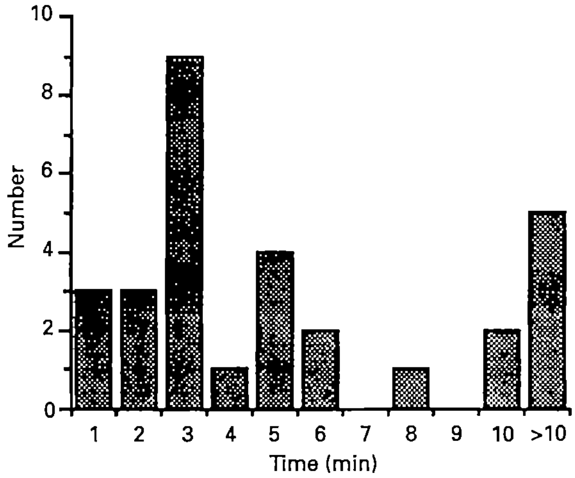

FIG. 1. Time to achieve adequate analgesia after subarachnoid injection.

from baseline, was treated with fluids and incremental doses of ephedrine. Any disturbance in fetal heart rate on routine fetal heart monitoring during the first 30 min was defined and recorded by the midwife.

If analgesia was inadequate at 10 min, the extradural catheter was used. The first dose of local anaesthetic given via the extradural catheter was always given by an anaesthetist. Because of the risk of intrathecal placement of the catheter, 0.25% bupivacaine 5 ml (12.5 mg) (a dose unlikely to cause a dangerously high block if given intrathecally [11]) was used in repeated boluses to achieve analgesia. The height of the block was again assessed by the anaesthetist 20–30 min after the extradural dose.

No restriction was placed on the management of the second stage of labour.

After delivery, subjects were seen each morning for 3 days to assess the presence of a postural headache.

RESULTS

We studied 30 patients (mean age 31 yr (range 23–44 yr), mean gestational age 39.7 (SD 1.3) weeks and at cervical dilatation mean 5.4 (1.9) cm before block). There were 29 multiparae and one primipara. Intrathecal placement of the spinal needle was successful at each attempt, with CSF outflow in 26 patients and a need to aspirate CSF in four.

Whilst all mothers had adequate sacral analgesia, abdominal analgesia was inadequate in five (16%) at 10 min because of inadequate cephalad spread. In those achieving adequate analgesia the median time to complete analgesia was 3 min (mean 4 (SD 2.4) min). Times to onset of adequate analgesia are shown in figure 1.

Eight women delivered without requiring additional analgesia. In these women the mean time from subarachnoid injection to delivery was 53 min (range 15–135 min). Seventeen mothers whose labour was of sufficient duration that they required additional analgesia had a mean duration of analgesia of 71 (21) min.

The median height of the block was T8 (range T4–L2). Maximum spread occurred in all patients by 15 min. All mothers except two had developed sympathetic block by 5 min. Both mothers who failed to develop a sympathetic block had inadequate abdominal analgesia. Motor block was extremely variable (table I).

TABLE I. *Degree of motor block 15 min after the subarachnoid injection.* n = *Number of mothers*

Motor block	*n*
0 = able to lift legs against gravity	6
1 = able to flex knee, unable to lift legs	12
2 = able to move feet, unable to flex knee	9
3 = no movement at all	3

Hypotension, responding to ephedrine less than 10 mg, occurred in two of the mothers (6%). Ephedrine was used prophylactically in one other patient, without any occurrence of hypotension. There was no fetal heart rate disturbance on the tocograph reported by the midwife.

Twenty-one mothers had the extradural catheters used to deliver 0.25% bupivacaine 10 ml. There were no blocks suggestive of an intrathecal placement of the catheter.

Spontaneous delivery occurred in 26 (86%) mothers, delivery occurring 15–400 min after the initial intrathecal block. The remaining women were delivered by forceps (three rotational, one outlet) for failure to progress. All babies were born in good condition with no Apgar score less than 7.

There were no headaches recorded on any of the first 3 days after delivery.

DISCUSSION

A few parturients deliver before their requested extradural has become established. This is more likely to occur if the recommended practice of giving small incremental doses of bupivacaine down the extradural catheter [12, 13] is followed. Carrie has recommended a maximum first dose of bupivacaine 12.5 mg [14]. This dose, given in a 10-ml volume, has been used intrathecally for Caesarean section without any dangerously high blocks [11]. Given i.v. over 30–60 s, plain bupivacaine 12.5 mg has been found to produce little effect [15]. Doubling of this dose to 25 mg in 10 ml (0.25%) has produced a total spinal block [16].

We have adapted the single space CSE to produce a safe, rapid and reliable onset of analgesia in labour. It is used routinely in our hospital for Caesarean section anaesthesia with a failure rate of 4% [5], although a rate of 30% has been reported using a 29-gauge needle [17].

We defined failure of the technique arbitrarily as painful contractions 10 min after the block; five women still had some abdominal discomfort at this stage. The median height of the block when it was deemed to have failed at 10 min was T12 (range T8–L2). All had substantial pain relief; however, this was not quantified with pain scores. Four of the five women had the analgesia extended uneventfully using the extradural catheter. The fifth received no extradural dose, and was pain free after 25 min. It is possible that the others would have been pain free by this time also.

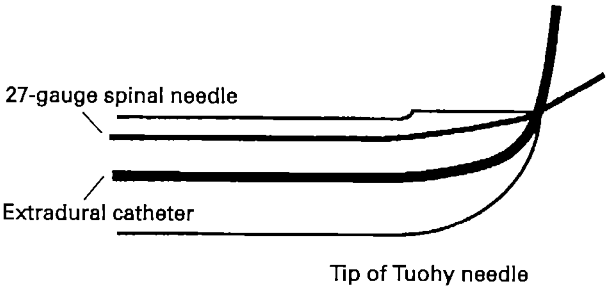

FIG. 2. Exaggerated representation of the relative courses taken by the extradural catheter and the spinal needle.

The range of dermatomal spread was from T4 to L2. Failure to reach an adequate height may have resulted from inadequate dosage or failure of cephalad spread of the local anaesthetic.

With any subarachnoid injection, it is possible to spill some of the dose into the extradural space. A small movement of the spinal needle during connection of the syringe or injection, might be enough to move part of the bevel out of the subarachnoid space. This is probably more likely with longer and finer needles which are more difficult to handle. Methods of attempting to prevent this movement involve marking the spinal needle with artery forceps [9] or a drop of fluid [18], so that relative movement between it and the introducing needle may be seen more easily. There was a need to aspirate CSF in two women in whom the block failed, which may indicate that the needle bevel was not located entirely in the subarachnoid space. Two failed blocks had features of too small an intrathecal dose, with no sympathetic block, very little spread and little motor block.

Inadequate height of block may also occur because plain bupivacaine used intrathecally is dependent on movement of CSF to achieve adequate rostral spread [19]. Carrie found that the spread of plain bupivacine was better if the patient was turned through 180° [4]. The required CSF movement may be achieved by expansion of the extradural veins, paravertebral muscle contraction or internal barbotage by the spinal nerve roots [4], all of which occur when the patient turns.

The presence of an extradural catheter allows treatment of inadequate analgesia, should this be necessary after the small intrathecal dose of bupivacaine. The catheter also allows continuation of analgesia for as long as is necessary.

Subarachnoid placement of the extradural catheter is a risk with this technique, and occurs in 3% of procedures at one centre [20]. There are those who advocate turning the needle between subarachnoid injection and catheter insertion [21–23] in an attempt to puncture the dura at a site different than that on which the catheter impinges. It should be noted that the force needed to perforate the dura is less if the needle is turned [24] and that turning the extradural needle may cause dural puncture [22, 25]; subarachnoid catheterization occurred in three of 77 patients in whom the needle was turned [22]. One centre found a rate of 3% increased to 17% when turning the needle was introduced [20]. We do not turn the extradural needle between spinal needle insertion and catheter insertion. The intrathecal catheter is more flexible than the spinal needle, and takes more of a deflection from the tip of the Tuohy needle. This might result in the needle and catheter hitting the dura at different points (fig. 2). In view of this, the incidence of intrathecal catheterization is perhaps less than might be expected. At Queen Charlottes Hospital, the single space CSE has been used routinely for spinal anaesthesia for more than 3 years without any recognized intrathecal catheterizations.

It is imperative that the first extradural dose on request for further analgesia is given by the anaesthetist. It is difficult to identify the effects of test doses against a background of residual analgesic block [14]. Aspiration is an unreliable means of detection of intrathecal placement [14, 26]. However, the danger of giving a massive intrathecal dose is not unique to the CSE technique. Total spinal blocks are an acknowledged complication of "top-ups" of previously normally functioning extradural catheters [26–28]. We elected to give a 12.5 mg dose at each increment until adequate analgesia had been achieved; thereafter, midwives observed the usual procedure using an incremental top-up technique.

Use of a combined spinal–extradural technique is associated with a small incidence of PLP headache in patients having Caesarean section [4–6, 29]. There was an insufficient number of patients in this study to permit the conclusion that headaches are not increased when the technique is used in labour. However, bearing down in the second stage of labour after lumbar puncture with a 22-gauge needle does not increase the incidence of PLP headache [3], and it seems unlikely that this may differ with a smaller needle.

With a single needle technique, decreased incidence of headache is achievable with the adoption of smaller needles [30], the use of non-cutting needles [31], keeping the bevel parallel with the dural fibres [10] and, possibly, by approaching the dura at a more acute angle [32] so that the holes in the dura and arachnoid do not overlap [33]. Factors in the decreased incidence of PLP headache with a single space CSE may be that as the spinal needle exits through the Tuohy needle it takes a cephalad deflection and therefore approaches the dura at more of an angle, and that the presence of the extradural catheter in the extradural space may splint the dura against the arachnoid membranes, thus minimizing fluid leak.

The disadvantage of the dose of subarachnoid bupivacaine we used is the degree of motor block suffered by some patients. However, this effect is not uncommon in pure extradural analgesia. The use of smaller doses of bupivacaine, perhaps with an opioid, may provide adequate analgesia without excessive motor block.

This technique requires attention from the anaesthetist, who should be readily available on the labour ward. This does not differ from recommended practice in extradural analgesia, which is contraindicated unless an anaesthetist can be available immediately to attend the mother [34].

A rapid, effective analgesic is of value for most mothers requesting regional analgesia. The spinal component of the CSE is especially appropriate in women complaining of perineal pain in labour, as extradural analgesia has a delayed sacral block [35]. The value of the extradural catheter is the ability to prolong analgesia or extend the block for operative delivery and treat inadequate intrathecal block. We believe that the lack of serious side effects, and the success of this technique in providing analgesia of rapid onset, justifies its use in those mothers needing analgesia in whom the time required to establish a good working extradural is a disadvantage.

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EFFECTS OF GIVING WATER 20–450 ML WITH ORAL DIAZEPAM PREMEDICATION 1–2 H BEFORE OPERATION

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SUMMARY

We have studied the volume of water which should accompany diazepam 10 mg oral premedication given 1–2 h before induction of anaesthesia in 75 patients undergoing elective gynaecological laparoscopy. Twenty-five patients were given 20 ml (group A), 25 patients 150 ml (group B), and 25 patients 300–450 ml of water (group C). There were no differences between the groups in gastric fluid volume and acidity. All groups reported a reduction in thirst and dryness of the mouth after water intake, while only group B reported significant anxiolysis. Eight patients in group C experienced augmented diuresis, compared with no patients in groups A and B. We conclude that 150 ml is the ideal amount of water given with oral premedication 1–2 h before anaesthesia. (Br. J. Anaesth. 1993; **71**: 503–506)

KEY WORDS

Surgery: day-case. Gastrointestinal tract: pH, volume. Anaesthesia: general.

In order to decrease the risk of aspiration of acid gastric content to the lungs, "nothing by mouth after midnight" has traditionally been recommended before general anaesthesia. Newer studies indicate that the period of fasting for clear fluids may safely be reduced to 2–3 h [1–3]. Unfortunately, the results have not been consistent as both a decrease [1, 2], no change [3, 4] and even an increase [5] in gastric fluid volumes have been reported with preoperative fluid intakes. Reduction in thirst and anxiety have also been described with preoperative intake of water [1–3]. The amount of water ingested with tablets may affect the rate and speed of absorption and thereby clinical effects of oral premedication [6]. There is no information on the effects of variable amounts of water given less than 2 h before induction of general anaesthesia, although this is when most patients receive oral premedication. We have therefore studied the effects on gastric content and patient wellbeing of varying the amount of water given with a standard oral premedication 1–2 h before induction of anaesthesia.

PATIENTS AND METHODS

The study was approved by the Regional Ethics Committee and each patient gave written informed consent. We studied 75 non-obese (< 130% of ideal body weight), ASA I and II patients undergoing day-case gynaecological laparoscopy under general anaesthesia. Patients with diseases known to affect gastric secretion and motility were excluded. All patients were asked to fast overnight and on their arrival in the hospital at about 07.00 the time of the last oral intake was recorded. The patients were then allocated randomly to receive diazepam (Valium tablets) 10 mg with 20 ml (group A), 150 ml (group B), 300 ml (group C) or 450 ml (group D) of cold water approximately 90 min before surgery.

After premedication, the patient remained in bed except for a mandatory visit to the bathroom to empty the bladder before transportation to the operating room. Despite this, it became apparent half-way through the study that eight of 25 patients in groups C and D had a full bladder, causing complaints from the surgical staff and requiring intraoperative catheterization. Several patients in group D also complained that they were required to drink a greater volume than they were used to. Athough no exclusions occurred for these reasons, we stopped the use of 300- and 450-ml volumes of water. As there were no significant differences in gastric content data or any of the other variables between patients having received 300 ml (15 patients) and 450 ml (10 patients), they were grouped together and analysed further as a new group C (300–450 ml).

We used a standard anaesthetic induction technique with atropine 0.5 mg, midazolam 2.5 mg, fentanyl 0.1 mg, thiopentone 250–375 mg and vecuronium 4 mg; the trachea was intubated using a 7.0-mm i.d. cuffed tube. Anaesthesia was maintained with enflurane and 67% nitrous oxide in oxygen. Immediately after tracheal intubation, an 18-French gauge Salem sump tube (Argyle) was passed orally into the stomach by a person blinded to study group. Gastric content was aspirated in a standardized manner shown previously to give reliable and accurate estimates of gastric fluid volume [7]. Gastric fluid pH was measured using Merck pH indicator strips [7].

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On arrival of the patient at the hospital, in the operating room and before leaving the recovery room, the patient assessed thirst, dryness of the mouth and anxiety and sedation using 10-cm visual analgoue scales (VAS) without subdivisions [8, 9]. When leaving the recovery room they also scored soreness of the throat in a similar fashion and were asked if they had experienced nausea or vomiting.

Gastric fluid volumes and pH were compared using analysis of covariance (ANACOVA), with ingestion–induction time and smoking (yes/no) as covariates [10]. Group comparisons of VAS values were also made with ANACOVA, using the initial values as covariate [10]. In order to identify variables affecting gastric fluid volume and acidity, backward stepwise multiple regression analyses [10, 11] were made using the variables age, smoking, fasting time (time from last oral intake at home), ingestion–induction time (time from premedication and water intake to induction of anaesthesia), amount of water intake and degree of anxiety before operation. Total correlations between gastric fluid volume and acidity were studied using Spearman's rank correlation [11]. Differences were taken as statistically significant at $P \leqslant 0.05$.

RESULTS

The groups were not significantly different in patient characteristics (table I) or gastric fluid volume and pH values (table II). Neither ingestion–induction time nor a history of smoking had any influence on the results for gastric content. No patient regurgitated or aspirated gastric content to the lungs.

All three groups reported significant reductions in thirst and dryness of the mouth (fig. 1). The reduction in thirst tended to be greater in groups B and C than in group A ($P = 0.08$). There were no differences in sedative effects and only group B reported a significant decrease in anxiety, with a 95% CI of 0.3–1.7 for the reduction (table III). After operation, there were no differences in thirst and dryness of the mouth (fig. 1), soreness of the throat (table III), or nausea (groups A and C, one patient; group B, two patients). None of the factors tested in the regression analysis was found to affect gastric fluid volume or pH significantly. Gastric fluid volume and pH values did not correlate in any of the groups.

TABLE I. *Patient characteristics (mean (range or* SD*)) (n = 25 each group). Except for intakes of water, no significant differences between the groups*

	Group A (20 ml)	Group B (150 ml)	Group C (300–450 ml)
Age (yr)	33 (20–43)	35 (19–47)	35 (23–44)
Weight (kg)	62 (9)	61 (8)	67 (10)
Height (cm)	166 (6)	165 (5)	167 (5)
Intake of water (ml kg^{-1})	0.33 (0.04)	2.38 (0.45)	5.47 (1.29)
Fasting time (h)	11 (2)	10 (2)	9 (1)
Ingestion–induction time (min)	94 (33)	88 (19)	89 (29)

TABLE II. *Gastric content (mean* (SD)*) (n = 25 each group). No significant differences between the groups*

	Group A (20 ml)	Group B (150 ml)	Group C (300–450 ml)
Gastric volume (ml)	31 (30)	23 (20)	23 (20)
Gastric pH	1.9 (1.0)	1.5 (0.3)	2.0 (1.1)
Patients with gastric volume $\geqslant$ 0.8 ml kg^{-1}	4	4	3
Volume $\geqslant$ 0.4 ml kg^{-1} and pH $\leqslant$ 2.5	11	8	7

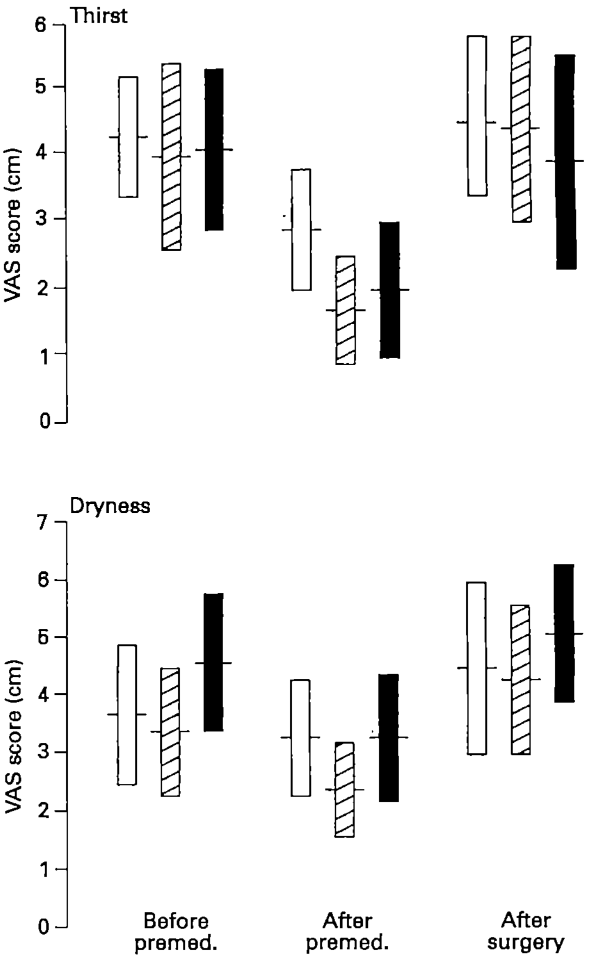

FIG. 1. Thirst and dryness of the mouth recorded on 10-cm visual analogue scales (VAS) in groups A (□), B (▨) and C (■) (mean values with 95% confidence intervals). Significant reductions over time in all groups, with groups B and C showing a tendency ($P = 0.08$) towards larger reductions in thirst than group A.

TABLE III. *Anxiety and sedation before and after premedication and water intake, and postoperative soreness of the throat (mean VAS scores* (SD)*) (n = 25 each group). * Significant decrease only in group B. † Significant increase within each group, without intergroup differences*

	Group A (20 ml)	Group B (150 ml)	Group C (300–450 ml)
Anxiety*			
Before	3.0 (3.0)	2.5 (2.4)	3.8 (3.1)
After	2.7 (3.3)	1.5 (1.6)	3.8 (3.2)
Sedation†			
Before	2.2 (2.8)	0.6 (0.8)	1.9 (2.9)
After	4.9 (3.5)	3.8 (3.0)	3.8 (2.7)
Sore throat	3.9 (3.1)	2.7 (2.3)	4.1 (3.5)

DISCUSSION

We found that the amount of water taken with diazepam premedication approximately 90 min before surgery neither decreased nor increased gastric fluid volume and acidity. This is in accordance with some [3, 4], but not all [1, 2, 5], earlier studies using greater intervals between fluid intake and induction of anaesthesia. Our study had a 80% power of detecting a difference in gastric fluid volumes between two of the groups corresponding to 75% of an SD of the results [11]. There was no correlation between gastric fluid volumes and pH values, implying that a dilution effect of large water intakes was not present. Hence, we could not confirm the speculation by McGrady and MacDonald [4] that a delay shorter than 2 h from water intake to anaesthesia would cause a decrease in both gastric fluid volume and acidity. Our results obtained with cold water should not be extrapolated to other clear fluids such as tea, coffee, soda water, apple or orange juice, as these fluids may have significantly different effects on gastric secretion, gastric emptying and oesophageal sphincter pressure during the first 2 h after ingestion [12–14].

A constant topic of discussion in previous studies [1–5] has been the underestimation of gastric fluid volume associated with blind gastric aspiration techniques. We used a standardized and validated blind aspiration technique [7] and were able to aspirate some gastric fluid in all our patients. Unlike most other workers, we also used a very homogenous study population and kept the patients supine in bed after water intake. This may be important, as both gastric emptying and gastric content vary with age, sex and body posture [15, 16]. Keeping the patients supine after water intakes may delay the start of gastric emptying [15]. Gastric volume tends to decrease with age [16], and women have slower gastric emptying rates than men [15].

As reported by others [1, 2], we found that water intake in the preoperative period reduced thirst. Both thirst and dryness of the mouth are subjective feelings influenced by many factors other than the amount and time of last fluid intake, and even small "sips" of cold fluid are able to reduce the appeasement of thirst and dryness of the mouth by mechanical, thermal and chemical stimulation of the oropharyngeal area [17, 18]. This may explain why 150 ml and 300–450 ml of water only tended to reduce thirst more than 20 ml. Similar to others [1, 2], we found that many patients did not report any reduction in thirst after water intake, thereby making it more difficult to demonstrate differences in the magnitude of thirst reduction. The lack of significant differences may, however, also have been attributable to a type II statistical error [11], as the reduction in thirst became significantly different when 20 ml was compared with the combined group receiving 150–450 ml.

Patients receiving water 150 ml had smaller anxiety scores compared with those given 20 or 300–450 ml. The amount of fluids ingested may have influenced the absorption of the diazepam tablets [1, 6] and thus the clinical effects. This seems unlikely, as the degree of sedation did not vary with the amount of water. The fact that 150 ml reduced anxiety compared with 20 ml is in agreement with Read and Vaughan [3], who found that free oral water intake until 2 h before operation reduced patient anxiety. They speculated that this was the result of interruption of positive feed-back loops of somatic manifestations of anxiety, or avoidance of restrictive regimens that increase the patient's perception of the danger involved. Why 150 ml was better than 300–450 ml is more difficult to explain. It is possible that being obliged to drink more than was wanted naturally, or experiencing a fast filling urinary bladder, made the patient more uncomfortable.

To our surprise, a significant number of patients drinking 300 or 450 ml of water were found to have a full urinary bladder during operation, despite having emptied the bladder before going to the operating room. We did not anticipate that this would be a problem, and therefore had to collect these data retrospectively. Eight of 25 patients is therefore a minimum number. This unsuspected phenomenon of a full bladder may be explained by induction of "water diuresis", which is known to start approximately 45 min after intake of large amount of fluids, causing an increase in urine output up to eight times normal for 2 h [17]. A literature search revealed a similar experience in a study of the effects of metoclopramide on emptying of gastric content [19]. This aspect of shortened fluid fast must be borne in mind, especially when fluids of known diuretic effect, such as coffee and tea, are ingested [20, 21].

In conclusion, based on the lack of negative effects on both gastric content and diuresis, and the associated decrease in thirst and anxiety, we believe that diazepam tablets given 1–2 h before anaesthesia should be ingested with 150 ml of cold water. The use of smaller or larger volumes of water seemed not to offer any advantages.

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PHARMACOKINETICS AND EFFECTS OF I.M. ALFENTANIL AS PREMEDICATION FOR DAY-CASE OPHTHALMIC SURGERY IN ELDERLY PATIENTS

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SUMMARY

We have studied the pharmacokinetics and effects of i.m. alfentanil as premedication for peribulbar block in 90 patients undergoing elective day-case cataract surgery. We compared alfentanil 12.5 μg kg^{-1} injected into the deltoid ($n = 30$*) or gluteal muscle (*$n = 30$*) 15 min before the peribulbar block, and placebo (*$n = 30$*). The alfentanil concentrations were significantly greater in the deltoid group during the study and the mean peak concentration occurred more rapidly in this group. Only alfentanil injected into the deltoid muscle reduced pain (assessed with a visual analogue scale (VAS)) associated with the peribulbar block. A mild sedative effect (VAS) was found in both alfentanil groups. We conclude that i.m. alfentanil appears to be a suitable premedicant for short, painful procedures because it has a short duration of action and is not associated with any clinically significant side effects.* (Br. J. Anaesth. 1993; **71**: 507–511)

KEY WORDS

Analgesics: alfentanil. Pharmacokinetics. Premedication.

Regional anaesthesia is used widely for outpatient cataract surgery because it provides excellent conditions for ophthalmic surgery and is associated with rapid recovery. In general, regional anaesthesia is accepted well by patients, but periocular injection of a local anaesthetic may produce pain and anxiety which may affect co-operation between the patient and the surgical team. Therefore, premedication may be beneficial, although it is not used routinely in day-case surgery [1, 2]. Benzodiazepines may produce undesirable effects in elderly patients, such as hypoxaemia [3] and excessive sedation [4]; as co-operation between patient and operative team is essential for successful management of ophthalmic surgery in regional anaesthesia, these may not be the drugs of choice in these patients. Pre-emptive analgesia may have a role in these circumstances, through use of opioid premedication [5, 6].

Alfentanil is a short acting opioid analgesic which has been shown to reduce pain 5–60 min after i.m. injection [7]. It has been shown previously that the site of i.m. injection affects the rate of absorption and the peak plasma concentrations of some drugs [8–10]. Therefore we decided to study the pharmacokinetics of alfentanil and its clinical effects in the elderly after i.m. administration into the deltoid or gluteal muscle as premedication for outpatient cataract surgery.

PATIENTS AND METHODS

After obtaining written informed consent, we studied 90 patients undergoing day-case cataract surgery with regional anaesthesia, in a randomized, placebo-controlled, double-blind investigation. The study was approved by the Ethics Committee of Turku University Hospital. The patients fasted for 9–10 h and arrived at the day surgical ward at 07.00. All the operations were performed at noon. Patients were allocated randomly to one of three groups. The deltoid group ($n = 30$) received alfentanil 12.5 μg kg^{-1} into the deltoid muscle, the gluteal group ($n = 30$) alfentanil 12.5 μg kg^{-1} into the gluteal muscle (upper outer quadrant of the buttock) and the placebo group ($n = 30$) 0.9% saline 1 ml (placebo) into the deltoid ($n = 15$) or gluteal ($n = 15$) muscle, 15 min before the block. The drug was injected by a nurse not participating in the study, using a 0.80 × 40-mm, 21-gauge × 40-mm needle (Braun, Sterican). Before administration of the drug, the following baseline recordings were made in the supine patient after at least 30 min of rest: heart rate (HR) using an oscilloscope (S&W Medico Teknik A/S, Albertslund, Denmark); systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures with an automatic device (Datascope Accutorr 2A, Datascope Corp., Japan); oxygen saturation (Sp_{O_2}) with a pulse oximeter (Datex Satlite Trans, Instrumentarium Corp., Helsinki, Finland). Subjective assessments of anxiety (extremes "calm–excited"), sedation ("alert–sleepy"), nausea ("no nausea–strong nausea") and pain ("no pain–excruciating pain") were measured with an ungraded visual analogue scale (VAS) of 0–100 mm.

Peribulbar block was performed by the anaesthetist with a solution of a local anaesthetic (2% lignocaine 5 ml with adrenaline 1:200000; 0.5% bupivacaine 5 ml; hyaluronidase 1 ml (150 iu)) exactly 15 min after the administration of the trial

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drug. The volume of local anaesthetic for the peribulbar block was 8 ml. Peribulbar injections were performed using 0.30 × 13-mm, 30-gauge × 13-mm (Microlance, Becton Dickinson) and 0.5 × 25-mm, 25-gauge × 25-mm (Neolus, Terumo) needles. A mechanical orbital compression device was applied on the orbit for 15 min with a pressure of 40 mm Hg (5.3 kPa). The pain associated with the block was assessed with a VAS immediately after injection (no pain–excruciating pain). HR, SAP, MAP, DAP and Sp_{O_2} were recored every 5 min and after operation every 15 min up to 1 h. Sedation and anxiety were measured with a VAS immediately before premedication, peribulbar block and surgery, and 0, 60 and 120 min after surgery.

Fifteen minutes after the block, the patient was transferred to the operation table. A flow of 100% oxygen 8 litre min^{-1} was directed under the surgical drapes during the operation.

The first 30 patients (10 in each group) aged more than 65 yr, were allocated randomly to the pharmacokinetic part of the study. Venous blood samples (5 ml) were obtained from the left cubital vein 0, 2, 5, 10, 15, 30, 60, 90, 120 and 180 min after premedication. Plasma was separated from the blood samples by centrifugation and stored at −20 °C until required for analysis of plasma concentrations of alfentanil, using a capillary gas chromatograph developed to allow rapid determination of the plasma concentration [11]. Assays were carried out at Orion Pharmaceutica, Espoo, Finland, using a Hewlett-Packard 5890A gas chromatrograph with an SE-30 capillary column (HNU-Nordion, Helsinki, Finland) and a nitrogen-sensitive detector. The limit of measurement was 2.0 ng ml^{-1}; intra-assay variability was 3.1, 6.8 and 5.0% at concentrations of 15, 7.5 and 2.5 ng ml^{-1}, respectively ($n = 5$–6) and interassay variability was 6.4, 3.0 and 14.4% for the same concentrations ($n = 5$–6). For each patient, the maximum plasma concentration (*C*max) and the time from administration to the maximum concentration (*tC*max) were determined.

Statistical analysis

Pharmacokinetic data were analysed using Student's *t* test. Differences between haemodynamic variables and Sp_{O_2} were tested using one-way analysis of variance followed by Student's *t* test. For VAS variables, Friedman's test followed by Wilcoxon's signed rank sum test were used to examine the differences between each time and the baseline value within groups; Kruskal–Wallis followed by Mann–Whitney *U* test were used for the differences between the groups.

The data are expressed as mean (SD) (demographic, haemodynamic parameters, Sp_{O_2} and pharmaco-

[redacted]

(table I) and baseline values of VAS variables (table II).

Pharmacokinetic variables

Mean (SD) plasma concentrations of alfentanil were significantly greater in the deltoid group at every time point (fig. 1). Mean maximum alfentanil concentration was 3.5 times greater in the deltoid group compared with the gluteal group (27.0 (8.7) ng ml^{-1} *vs* 8.7 (2.5) ng ml^{-1}; $P < 0.001$) (table III). In addition, absorption was more rapid in the deltoid group: *tC*max 19.5 (15.4) min compared with 64.5 (48.0) min in the gluteal group ($P = 0.018$).

Haemodynamics and Sp_{O_2}

The peribulbar block was associated with an increase in heart rate. The smallest increase occurred in the deltoid group (2.1 (3.6) beat min^{-1}) and the greatest in the placebo group (6.6 (8.1) beat min^{-1}) ($P = 0.024$). Otherwise, haemodynamic state was stable and the groups were comparable (fig. 2). No significant changes in Sp_{O_2} occured (fig. 2).

Pain, sedation, anxiety and nausea

Pain scores associated with the peribulbar block were least in the deltoid group (VAS median 23, range 5–60 compared with placebo ($P = 0.034$); 95% confidence limit for difference 0.9–18.0).

TABLE I. *Patient characteristics (mean (range or SD)). No statistically significant differences between groups*

	Deltoid group ($n = 30$)	Gluteal group ($n = 30$)	Placebo group ($n = 30$)
Age (yr)	71.3 (44–83)	69 (44–84)	68.2 (50–83)
Weight (kg)	72.9 (11.9)	68.1 (10.8)	72.4 (14.0)
Sex (M:F)	8:22	6:24	14:16
ASA (I/II/III)	0/14/16	2/17/11	4/11/15
Preoperative			
HR (beat min^{-1})	73.0 (10.8)	70.6 (10.1)	72.6 (14.4)
SAP (mm Hg)	162.7 (25.4)	163.5 (19.7)	162.7 (19.0)
MAP (mm Hg)	113.2 (14.6)	115.4 (12.4)	113.2 (12.4)

TABLE II. *Subjectively estimated sedation and anxiety (median (range)) after i.m. alfentanil 12.5 μg kg^{-1}. Visual analogue scale (VAS): 0 = alert...100 = sleepy; 0 = calm...100 = excited.* $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ *compared with baseline*

	Deltoid group	Gluteal group	Placebo group
Sedation			
0 min	0 (0–60)	0 (0–65)	0 (0–50)
15 min	9 (0–80)*	20 (0–90)	0 (0–82)
30 min	20 (0–95)**	29 (0–95)*	0 (0–64)
After op.			
0 min	14 (0–95)*	20 (0–95)*	0 (0–30)

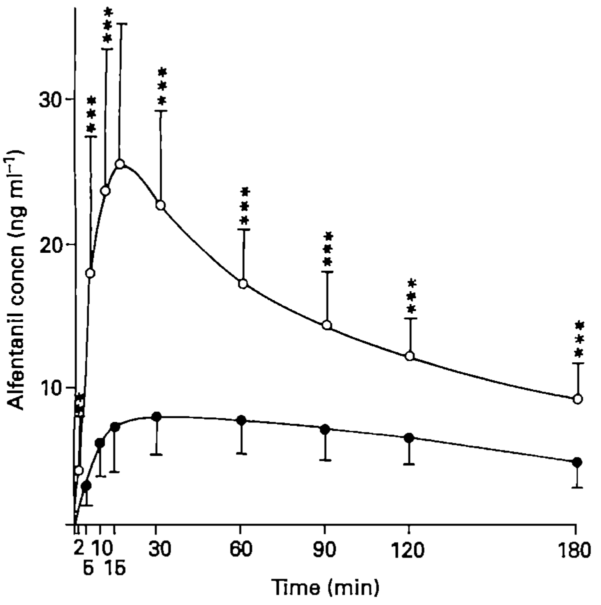

FIG. 1. Mean (SD) alfentanil concentrations after i.m. injection of alfentanil 12.5 $\mu g\ kg^{-1}$ to the deltoid (○) or gluteal (●) muscle. $^{**}P < 0.01$; $^{***}P < 0.001$ between groups.

TABLE III. *Pharmacokinetic study. Patient characteristics and plasma pharmacokinetic variables after injection of alfentanil into deltoid or gluteal muscle (mean (SD) [range]). CI 95% = 95% confidence limit. ns = Not significant*

	Deltoid group (n = 10)	Gluteal group (n = 10)	P
Age (yr)	74.4 [68–83]	74.3 [65–84]	ns
Weight (kg)	74.6 (13.7) [60–100]	63.0 (10.1) [45–82]	ns
Sex (M:F)	2:8	0:10	ns
Cmax (ng ml^{-1})	27.0 (8.7)	8.7 (2.5)	< 0.001
CI 95%	21.1–32.8	6.9–10.5	
tCmax (min)	19.5 (15.4)	64.5 (48.0)	0.018
CI 95%	8.5–30.5	30.2–98.8	

Alfentanil injected in the gluteal muscle (VAS 31, 1–70) was comparable to placebo (32, 13–90). A significant sedative effect compared with baseline VAS occurred in the deltoid group 15 min after premedication (P = 0.011), continuing until the end of operation (table II). In the gluteal group, sedation was observed 30 min after premedication and lasted until the end of operation. Placebo did not have any sedative effect during the study. Anxiety compared with baseline decreased 15 min after premedication in both the alfentanil groups (deltoid group, P = 0.030; gluteal group, P = 0.002). In the placebo group, anxiety was reduced only after operation (P < 0.001). The decline of anxiety in the gluteal group differed from placebo 15 min after premedication (P = 0.008).

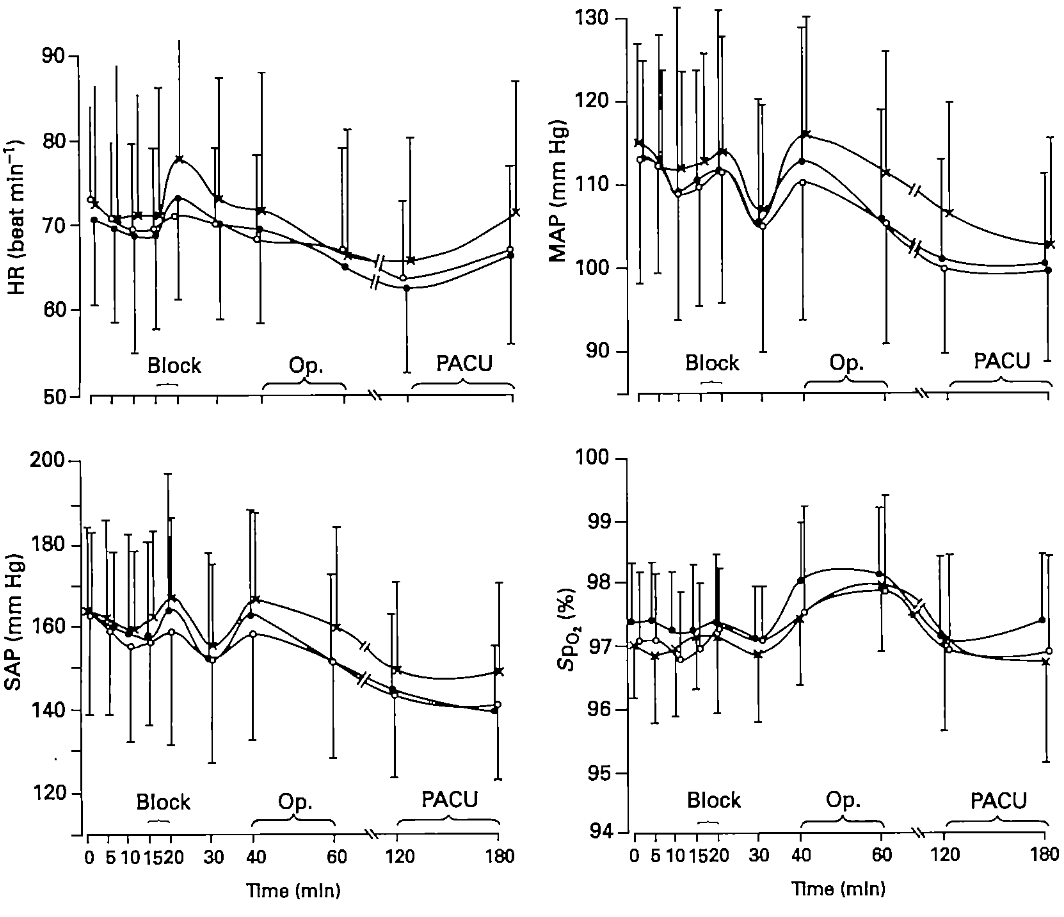

FIG. 2. Haemodynamic variables and oxygen saturation (Sp_{O_2}) (mean (SD)) before and after i.m. injection of alfentanil 12.5 $\mu g\ kg^{-1}$ in the deltoid (○), gluteal (●) and placebo (×) groups. HR = heart rate; SAP = systolic arterial pressure; MAP = mean arterial pressure; Block = peribulbar block; Op. = operation; PACU = post anaesthesia care unit.

One patient in the deltoid group experienced nausea and one patient in the placebo group who was very anxious, was given extra medication (alfentanil) before operation and excluded from the study.

DISCUSSION

The role of routine premedication in outpatient surgery is not clear [12, 13] and further clinical studies are needed. In this placebo-controlled, double-blind study we showed that i.m. alfentanil was superior to placebo, especially when injected into the deltoid muscle. Deltoid administration was associated with a fast onset but short duration of action. This is a useful property, especially in day-case surgery. Only alfentanil injected in the deltoid muscle was able to reduce the pain associated with the peribulbar block. A mild sedative effect, a maximum 30 min after premedication and lasting up to the end of operation, was seen in both alfentanil groups. Alfentanil also diminished anxiety associated with the peribulbar block and operation.

Are there any advantages of i.m. opioid administration compared with the more common i.v. use of opioids in premedication before anaesthesia? Opioid premedication has been shown to reduce intra- and postoperative requirements for analgesics [1, 2]. However, postoperative nausea and vomiting are common problems associated with the i.v. use of opioid analgesics in outpatient surgery. Vomiting is especially harmful during intraocular surgery, because straining can increase the intraocular pressure and lead to loss of vitreous. In a study by Shafer and colleagues, the incidence of postoperative nausea was 42 % and that of vomiting 23 % after i.v. opioid premedication [14]; in our study, only one patient had nausea after operation and none of the patients vomited. All the patients were co-operative and dizziness or drowsiness did not occur. This is in accordance with others [7, 15] who have reported that nausea, vomiting and dizziness occur less often after i.m. alfentanil compared with other opioids. It is possible that the degree of nausea and vomiting after opioid administration is dose-dependent, small doses producing an antiemetic effect, while larger doses may cause nausea and vomiting [16, 17]. A similar biphasic dose–response curve has been described with pethidine; doses less than 1 mg kg^{-1} i.m. were associated with an antiemetic effect, but doses greater than 1 mg kg^{-1} caused nausea and vomiting [18]. After i.m. injection of alfentanil, absorption is more even and large peak concentrations with clinically significant side effects are avoided compared with i.v. injection. This is consistent with the small and non-significant changes in Sp_{O_2} and haemodynamic variables in our study.

The site of injection may be important. Grabinski and colleagues found that morphine is absorbed much faster and better if administered into the deltoid muscle than into the gluteal muscle [19], while in the study by Kirkpatrick, Henderson and Nimmo, the absorption of morphine from deltoid and gluteal sites was similar [20]. Diazepam is absorbed faster from the deltoid muscle compared with the vastus lateralis muscle [9].

In our study, the absorption of alfentanil was more rapid and apparently more complete after injection into the deltoid muscle. The time to the mean peak concentration was three times longer in the gluteal group. In that group, the alfentanil concentrations remained small during the study period and the mean peak concentration was 30 % of that in the deltoid group. The reason for this finding may be greater blood flow in the deltoid muscle [8], injection partly into the subcutaneous fat in the gluteal region, or both. In the deltoid group, *t*Cmax was comparable to that observed by Chauvin and colleagues in middle-aged subjects [15].

We conclude that alfentanil injected into the deltoid muscle may be used safely in short, painful procedures and as premedication in day-case surgery in elderly patients.

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SKIN CONDUCTANCE RESPONSES TO AUDITORY STIMULI AND ANTICIPATORY RESPONSES BEFORE VENEPUNCTURE IN PATIENTS PREMEDICATED WITH DIAZEPAM OR MORPHINE

S. M. GEDDES, W. M. GRAY, K. MILLAR AND A. J. ASBURY

SUMMARY

We have measured the skin conductance response to innocuous auditory stimuli and the anticipatory response before venepuncture in 45 patients receiving diazepam, morphine or no premedication before general anaesthesia. Subjective ratings of anxiety and sedation were measured using visual analogue scales. Skin conductance was less in subjects receiving diazepam than in the other groups, and the pattern of change of skin conductance in this group indicated superior adaptation to the environment during presentation of the innocuous stimuli compared with the other groups. After warning of venepuncture there was a large increase in skin conductance in all groups. There was a significant relationship between anxiety and skin conductance in unpremedicated patients and those receiving diazepam. (Br. J. Anaesth. 1993; **71**: 512–516)

KEY WORDS

Premedication: diazepam, morphine.

Anxiety is an unpleasant emotional experience which is widespread in patients awaiting surgery. One of the aims of premedication is to reduce its intensity. Anxiety is a subjective concept and is most often measured by self-report. However, tests of emotional, behavioural or physiological arousal can be used to support the subjective rating. Heart rate [1], digital blood flow [2–4], simple measures of skin conductance [5] and plasma [1, 4, 6] and cerebrospinal fluid [1] catecholamine concentrations have been used in the assessment of preoperative anxiety and the effects of premedication.

Skin conductance reflects eccrine sweat gland activity and associated changes in the epidermis, and hence activity in the sympathetic sudomotor fibres [7]. Measurement of skin conductance has been used extensively in the psychophysiological investigation of anxiety and, more recently, the effects of anxiolytic and other psychotropic agents. The effect of morphine on skin conductance has not previously been studied.

The skin conductance waveform can be described by the baseline skin conductance level (SCL) and by the frequency of superimposed peaks (non-specific responses (NSR)) [7]. Both are increased in anxiety states [8, 9]. Presentation of an external stimulus evokes a skin conductance response (SCR), which is superimposed on the SCL and NSR. If a series of identical stimuli is presented, there is a progressive decrease in SCR amplitude until no response occurs (habituation). Subsequent presentation of a novel stimulus usually results in a large amplitude SCR (dishabituation) [10]. Habituation is slower, and dishabituation more reliably elicited, in anxious subjects [9]. Conversely, rapid habituation and a low incidence of dishabituation indicates that the subject has adapted readily to his environment. The change in SCL during presentation of a series of stimuli also reflects emotional arousal and adaptation [9].

It may be predicted that effective anxiolytic medication would reduce SCL and NSR, and that the change in SCL with time and rate of habituation would indicate superior adaptation to the environment compared with the unmedicated subject.

The first objective of this study was to investigate the differences in absolute values and patterns of change in skin conductance between unpremedicated patients, patients premedicated with diazepam and those premedicated with morphine under innocuous and stressful conditions. A second objective was to examine the relationship between these measures and subjective ratings of anxiety and sedation.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. Informed consent was obtained from 45 patients undergoing elective orthopaedic or general surgical procedures under general anaesthesia. Exclusion criteria were pregnancy, age greater than 65 yr, neurological disease, diseases with potential neurological complications (e.g. diabetes), operations for malignancy, psychiatric illness, treatment with drugs with a sedative or anticholinergic action, and treatment with beta-blockers. Patients were excluded if they failed a simple clinical hearing test.

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On the morning of surgery, the patient's anxiety and degree of sedation were assessed using 10-cm visual analogue scales (VAS). The extremes of the anxiety VAS were designated "completely calm" and "the most worried I can ever imagine being"; those of the sedation VAS were "wide awake" and "so drowsy I cannot keep my eyes open". Patients were then allocated randomly to one of three groups. Approximately 90 min before surgery group D received diazepam 10 mg orally and group M received morphine 10 mg intramuscularly. Group ND (no drug) received no premedication on the ward, but had been informed at the time of recruitment that they would receive i.v. sedation with midazolam after completion of the study and approximately 40 min before anaesthesia and surgery.

Patients in groups D and M were studied 60–70 min after premedication, and those in group ND 40–50 min in advance of the time at which they would normally have been brought to theatre. On arrival in the theatre suite, patients rated anxiety and sedation as before, under the supervision of a nurse who was unaware of their study group.

Recording took place in a quiet, artificially-illuminated room adjacent to the theatre suite. Ambient temperature was 21–24 °C. Skin conductance was measured using an SC4 skin conductance coupler (Contact Precision Instruments) interfaced with an Amstrad PC1512 microcomputer. The sampling frequency was 10 Hz. The absolute accuracy of the SC4 coupler is 0.3 microsiemens (μS) and the maximum resolution is 0.003 μS. The minimum response criterion used in this work was 0.03 μS.

Two silver–silver chloride cup electrodes, each with a contact area of 0.8 cm^2, were attached to the palmar surfaces of the middle phalanges of the second and third digits of the patient's non-dominant hand. The non-abrasive electrolyte paste, which was prepared by the hospital pharmacy, contained sodium chloride 0.05 mol $litre^{-1}$ [11]. Ten minutes was allowed for the electrodes to settle; patients rested quietly during this time.

Computer software had been developed (by S.M.G.) using Microsoft QuickBASIC v4.5 to provide an on-line display of the skin conductance waveform and to record the digitized data on disk. Computer-generated tones had been recorded using the Audiocard 300E (Speech Design). During recording of skin conductance, these tone files were called by the controlling program and replayed by the audiocard; thus recording of skin conductance data was not interrupted during the period of greatest interest immediately after stimulus presentation.

Skin conductance responses

Auditory stimuli recording (*ASR*). Patients lay supine with the eyes open and were informed that they would hear a series of "beeps". They were assured that there was no associated task requirement. Skin conductance was recorded for an initial period of 3 min when no stimuli were presented, during presentation of the auditory stimuli via occlusive headphones over 3 min and finally for 3 min with no stimuli. The stimuli comprised 11 tone pairs presented at 80 dB. Each tone lasted 0.8 s and the interval between the tones was 0.1 s. Tone pairs 1 to 10 were identical (1024 Hz and 634 Hz). The 11th pair consisted of the familiar first tone followed by a novel tone (1024 Hz and 380 Hz). In order that the patient could not anticipate stimulus presentation, the interstimulus intervals varied (10, 15 or 25 s); however, the presentation sequence was identical for each subject.

Anticipatory response before venepuncture. The patient was informed that an i.v. cannula was to be inserted. Immediately after this, skin conductance was recorded for 60 s, ending just before venepuncture.

Data analysis

The digital recordings of skin conductance were analysed using computer software, written (by S.M.G.) using Microsoft QuickBASIC v4.5, which allowed replay of the digitized data and display of the skin conductance waveform with automatic measurement and display of values of SCL and response amplitude. Differentiation between evoked SCR and NSR was by on-screen display of a "latency window" from 1 to 4 s after stimulus presentation.

An observer who was unaware of the patient allocation recorded the following measurements. The number of NSR greater than 0.03 μS in each of the recordings for each subject; SCL at the start of the ASR, immediately before presentation of stimuli 1, 2, 6 and 10, and the final value; SCL immediately before and 60 s after warning of venepuncture; the number of auditory stimuli which elicited an SCR greater than 0.03 μS before two consecutive stimuli failed to evoke an adequate response (the criterion for habituation used in this paper [12]); the occurrence of an SCR following presentation of the novel (11th) stimulus (dishabituation). If the patient had responded to the 10th stimulus, he was considered to have dishabituated only if the response to the 11th stimulus was greater than the preceding one.

Analysis of the serial measurements of SCL was carried out in accordance with the guidelines of Matthews and colleagues [13]. The area under the curve (AUC) of the graph of SCL *vs* time was calculated for each subject during the ASR, using the values of skin conductance measured at the six points described above, and during the 60 s before venepuncture, using the initial and final values of conductance. These values were used as summary measures of skin conductance and were considered further.

Differences between the groups for VAS, NSR and AUC were identified using the Kruskall–Wallis test. These were examined further using the Mann–Whitney test. Rate of habituation and the incidence of dishabituation in response to the novel stimulus were examined using the chi-square test. The Bonferroni correction was applied to offset the increased risk of type 1 error inherent in multiple comparisons, hence $P < 0.017$ was considered significant (i.e. 0.05/number of comparisons). Within-group changes in SCL and NSR were analysed using the Wilcoxon matched-pairs rank sum test. Relationships between variables were examined using the Spearman rank correlation coefficient. In these cases $P < 0.05$ was considered significant. All values of P are two-tailed.

Minitab (Release 6.1.1), run on an Amstrad PC1512 microcomputer, was used for data analysis.

RESULTS

The groups were similar in sex ratio, age, height and weight (table I).

Skin conductance during ASR

The number of NSR in the ASR was similar in groups M (median 25, inter-quartile range (IQR) 9–39) and ND (median 26, IQR 14–45). The number occurring in group D (median 4, IQR 3–13) was significantly smaller than in group M ($P = 0.012$) and in group ND ($P = 0.0008$, Mann–Whitney test).

In groups M and ND, mean SCL increased after the first stimulus and remained greater than the initial value throughout the recording, but the changes from initial to final value were not significant. In group D, SCL decreased progressively during the ASR and the change was significant (median change -1.18 μS, $P = 0.005$, Wilcoxon matched-pairs rank sum test).

TABLE I. *Patient characteristics (mean (range or SD))*

	Sex (M:F)	Age (yr)	Height (m)	Weight (kg)
Group D ($n = 15$)	9:6	37 (19–59)	1.68 (0.14)	69.1 (10.1)
Group M ($n = 15$)	8:7	36 (19–61)	1.70 (0.11)	72.9 (16.9)
Group ND ($n = 15$)	6:9	38 (19–59)	1.67 (0.12)	66.3 (11.5)

TABLE II. *Number of subjects in each group producing a low (0–3), medium (4–6) or high (7–10) number of SCR to the auditory stimuli before habituation, and the number in each group who dishabituated following the novel stimulus*

	Responses before habituation			Response to novel stimulus	
	0–3	4–6	7–10	Yes	No
Group D	9	4	2	7	8
Group M	6	3	6	12	3
Group ND	3	3	9	12	3

TABLE III. *Number of NSR occurring in the final 60 s of the ASR (Pre-warning) and in the 60 s after warning of venepuncture (Post-warning) (median (interquartile range))*

	Pre-warning	Post-warning
Group D	1 (0–2)	9 (8–11)
Group M	4 (1–6)	12 (7–13)
Group ND	6 (0–6)	11 (11–12)

TABLE IV. *Area under the curve of the graph of skin conductance vs time in the final 60 s of the ASR (Pre-warning) and in the 60 s after warning of venepuncture (Post-warning) (median (interquartile range))*

	Pre-warning (μS.min)	Post-warning (μS.min)
Group D	3.31 (1.76–4.37)	7.44 (5.55–10.8)
Group M	7.25 (5.28–8.22)	12.84 (7.54–14.46)
Group ND	7.18 (5.23–12.39)	12.49 (8.73–15.07)

The median value of the AUC of the graph of SCL *vs* time in group D was 30.77 μS.min (IQR 20.71–54.47). This was significantly smaller than the values in group M (median 61.61, IQR 36.70–72.53, $P = 0.009$) and group ND (median 60.93, IQR 54.60–102.80, $P = 0.0004$, Mann–Whitney test).

Habituation and dishabituation of the SCR

The patients were arbitrarily defined as low (0–3), medium (4–6) or high (7–10) responders on the basis of the number of the last stimulus which elicited an SCR before two consecutive "no-responses" (habituation). Dishabituation was defined as above. There were no differences between the groups in both respects (chi-square test) (table II).

Anticipatory response

The number of NSR in the 60 s after warning of venepuncture (table III) was significantly smaller in group D than in group ND ($P = 0.005$, Mann–Whitney test). In all groups, the number of NSR occurring in this period was significantly greater than that recorded during the last 60 s of the ASR ($P = 0.001$ in all groups, Wilcoxon matched-pairs rank sum test).

There were no significant differences between groups in AUC during the 60 s in anticipation of venepuncture (Mann–Whitney test) (table IV). These values of AUC were compared with the values for AUC in the final 60 s of the ASR: there was a significant ($P < 0.002$) increase in all groups (Wilcoxon matched-pairs rank sum test).

Anxiety scores

Initial anxiety and sedation scores were similar in all groups (table V). The increase in anxiety score in group ND was significant ($P = 0.025$, Wilcoxon matched-pairs rank sum test) and the final score in this group was significantly greater than that in group D ($P = 0.013$, Mann–Whitney test).

There were significant increases in sedation scores in groups D ($P = 0.020$) and M ($P = 0.014$, Wilcoxon matched-pairs rank sum test), but there were no significant differences between the groups in respect of final sedation score.

Correlation between skin conductance and subjective variables

Spearman rank correlation coefficients, describing the relationships between the final ratings of anxiety and sedation and various measures of skin conductance recorded during the ASR described above, plus the initial value of SCL, were calculated for individual groups.

In group D, there was a significant correlation between the decrease in SCL during the ASR and the anxiety score ($r_s = 0.56$, $P = 0.035$). In group ND there were significant correlations between the anxiety score and the number of NSR ($r_s = 0.60$,

TABLE V. *VAS scores (median (interquartile range)) for anxiety and sedation before pre-medication (initial) and on arrival in the theatre suite (final)*

	Anxiety (mm)		Sedation (mm)	
	Initial	Final	Initial	Final
Group D	19 (7–46)	25 (20–31)	4 (1–16)	23 (2–29)
Group M	15 (6–32)	23 (10–37)	6 (2–16)	33 (7–66)
Group ND	26 (10–36)	35 (30–53)	4 (3–7)	5 (0–20)

$P =$ 0.019) and the change in SCL during the ASR ($r_s = 0.55$, $P = 0.033$). In the same group there was a significant negative correlation between the change in SCL and the final sedation score ($r_s = -0.58$, $P = 0.022$).

DISCUSSION

In general, skin conductance was less and showed a pattern indicating superior adaptation to the environment during the ASR in patients who received diazepam compared with those receiving morphine or no premedication. Similar effects of diazepam on skin conductance have been demonstrated in patients with anxiety disorder [14] and in stressed volunteers [15].

Although there appeared to be some depression of skin conductance by morphine, none of the indices was significantly different from those recorded from the patients who had received no premedication. In addition to their specific central nervous system effects, opioids produce a generalized decrease in arousal by their action on the central noradrenergic activating systems arising in the nucleus coeruleus in the midbrain. However, morphine had little effect on skin conductance, suggesting that skin conductance is not a non-specific index of sedation or anxiolysis, but may be more sensitive to certain groups of drugs, for instance those which act by facilitating GABA-ergic transmission. This idea is supported by the finding that cyclobarbitone causes a profound depression of skin conductance [16]; barbiturates facilitate GABA-ergic transmission via an action at specific receptor sites within the GABA receptor complex [17, 18].

Rate of habituation and the occurrence of dishabituation appeared less sensitive to the effect of diazepam than the other measures, but this may reflect insensitivity of our test. In a pilot study in surgical patients, habituation had occurred in all subjects by the seventh stimulus. However, several patients in groups M and ND had not habituated after 10 stimuli, resulting in a ceiling effect. A larger number of stimuli might have allowed greater differentiation between the groups.

Benzodiazepines suppress other measures of sympathetic nervous system activity in patients awaiting surgery. Cerebrospinal fluid catecholamine concentrations were smaller in patients receiving diazepam than in unmedicated patients and those receiving placebo [1], and plasma adrenaline concentrations were reduced after administration of chlordemethyldiazepam [4]. However, an increase in plasma adrenaline concentration following premedication with diazepam has been reported [6]. It is interesting that these authors found no increase in plasma adrenaline in patients who received papaveretum and hyoscine.

Oral nitrazepam [2] and oral chlordemethyldiazepam [4] produce cutaneous vasodilatation as measured by digital pulse–volume plethysmography. Conversely, vasoconstriction is present in patients premedicated with pethidine and promethazine and those receiving papaveretum and hyoscine [3]. Anxious subjects have a high vasoconstrictor and sudomotor tone, resulting in a "cold sweat". Thus it appears that benzodiazepines reduce both components of this familiar symptom of anxiety, whilst opioids are less effective.

Physiological changes occurring in anticipation of a threatening stimulus are a useful measure of anxiety. Fell and his co-workers [6] found that plasma adrenaline and noradrenaline concentrations were within the normal range after venepuncture in volunteers and suggested that venous cannulation did not produce a measurable stress response. We recorded a large increase in both the number of NSR and the SCL before venepuncture in all groups, and the suppression of skin conductance by diazepam became less marked. Where a prolonged recording was made after venepuncture, the increase in skin conductance was sustained for at least 5 min. The occurrence of a detectable response in our patients may reflect the greater levels of anxiety present in patients compared with volunteers, or a difference in sensitivity between the two techniques.

In surgical patients, significant correlations have been demonstrated between increases in plasma adrenaline and anxiety [6], and between heart rate and anxiety [1, 19]. We found significant correlations between anxiety and number of NSR in group ND, the change in SCL during the ASR in groups D and ND, and a negative correlation between sedation and change in SCL in group ND. These correlation coefficients were of magnitude similar to those reported between anxiety and various measures of skin conductance in stressed volunteers [20] and anxious patients [9]. The absence of any significant relationship between the subjective measures and skin conductance in group M supports our earlier observations about the lack of a relationship between the perceived anxiolytic or sedative effects of morphine and skin conductance.

Lader has suggested that NSR frequency is the best index of emotional arousal [8]. We found this to be true in unpremedicated subjects, but found that the change in SCL over the duration of the recording was also related to anxiety scores. To our knowledge the use of the AUC of the graph of SCL *vs* time has not been used previously in the analysis of skin conductance data. It is interesting that this summary measure, representing total skin conductance activity, was not related to either of the subjective measures in any group.

It is recognized that anxiolysis and sedation are separate psychopharmacological effects. We asked our subjects to rate both anxiety and sedation, as we wished to investigate whether measurement of skin conductance could differentiate between the two. We found no evidence to support this idea.

In conclusion, this study has shown that administration of diazepam to surgical patients produces a pattern of skin conductance consistent with a lower level of autonomic arousal and greater adaptation to the environment than in unpremedicated subjects and those receiving morphine. We suggest that skin conductance might be more sensitive to drugs facilitating GABA-ergic transmission than to drugs producing anxiolysis or sedation primarily by other mechanisms. We consider that measurement of skin conductance may be useful in the evaluation of other anxiolytic and sedative drugs in anaesthesia.

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NAUSEA AND VOMITING AFTER GYNAECOLOGICAL SURGERY: A META-ANALYSIS OF FACTORS AFFECTING THEIR INCIDENCE

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SUMMARY

A total of 1442 patients who had major gynaecological surgery were recruited into three multicentre studies using a standard general anaesthetic technique in order to assess the efficacy of various doses of orally administered ondansetron in the prevention of postoperative nausea and vomiting. A total of 1257 patients were included in this analysis: 420 received oral formulations of placebo and 212, 296 and 329 received ondansetron 1, 8 and 16 mg, respectively. The following factors were measured in these studies and were considered to have a possible influence on the proportion of patients experiencing postoperative nausea and vomiting: age of patient; volatile anaesthetic; intraoperative dose of fentanyl; postoperative dose of morphine; country; anaesthesia duration; neuromuscular blocker; neuromuscular block antagonist; premedicant; recovery time; type of surgery; antiemetic treatment; body weight. Using a process of elimination based on logistic regression techniques, the factors found to be the most important influences on the frequencies of nausea and vomiting were antiemetic treatment, type of surgery, neuromuscular blocker, country, volatile anaesthetic and age. A statistically significant interaction between type of surgery and age was observed. Adjusted probabilities of nausea and vomiting were obtained from the model, including all the above factors, together with the type of surgery by age interaction. Ondansetron 8 mg showed the smallest adjusted probability of nausea (0.54) and vomiting (0.34) and placebo the greatest (nausea 0.75, vomiting 0.61). A similar pattern of adjusted probabilities over neuromuscular blocking agents was seen for nausea and vomiting, with the greatest occurring in patients receiving pancuronium (nausea 0.74, vomiting 0.57) and the least in patients receiving alcuronium (nausea 0.59, vomiting 0.38). For country effects, the United Kingdom exhibited the greatest adjusted probability of nausea (0.75) and vomiting (0.54) and Germany the smallest (nausea 0.49, vomiting 0.34). Adjusted probabilities of nausea and vomiting were similar for enflurane and isoflurane. With increasing age, the adjusted probabilities of postoperative nausea and vomiting appeared to increase for patients having abdominal hysterectomy and laparotomy. This pattern was not repeated in patients having vaginal hysterectomy. (Br. J. Anaesth. 1993; **71**: 517–522)

KEY WORDS

Vomiting: antiemetics, incidence, nausea. Pharmacology: ondansetron.

Postoperative nausea and vomiting are distressing and common occurrences after operative procedures requiring general anaesthesia [1]. It is believed that the frequencies of their occurrence have changed little in the past 30 years [1]. Many factors are thought to influence the frequencies, including the age of the patient, body weight, type of surgical procedure and the anaesthetic agents and techniques used [1, 2]. However, much of the evidence for variations in the frequencies of postoperative nausea and vomiting is not well documented. Indeed, studies published to date have often involved small numbers of patients and have used a variety of methodologies which have made it difficult to reach a clear consensus on the most important factors. Gynaecological surgery has been used often as a model in the evaluation of antiemetic drugs, yet little is known about the frequencies of nausea and vomiting associated with the various types of surgery involved. A series of multicentre clinical trials has recently been conducted in countries throughout Western Europe, to examine the efficacy of orally administered ondansetron (as ondansetron hydrochloride dihydrate) in the prevention of postoperative nausea and vomiting.

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PATIENTS AND METHODS

Three multicentre, randomized, double-blind, placebo-controlled studies were conducted in seven countries throughout Western Europe. All had Regulatory and local Ethics Committee approval, and informed consent was obtained from each patient. The methodologies used in each study were identical. Patients aged 18–65 yr were studied, undergoing major gynaecological surgery using a standard general anaesthetic technique. Patients who were classed as ASA IV and V were excluded, as were patients who weighed less than 45 kg or more than 90 kg and those who were pregnant or breast feeding. In addition, patients who had experienced vomiting or who had taken antiemetic treatment during the previous 24 h were excluded. The use of intragastric tubes after operation was not permitted.

Patients were allocated randomly to receive one of three doses of active medication or placebo. Study medication was administered orally, the first dose approximately 1 h before induction of anaesthesia and the second and third doses 8 and 16 h after the first. Of 1442 patients recruited to the three studies, 1257 were evaluated: 420 received placebo and 212, 296 and 329 received ondansetron 1, 8 and 16 mg, respectively.

Premedication comprised temazepam 10–30 mg or diazepam 5–20 mg, administered either orally or rectally. Anaesthesia was induced using i.v. thiopentone 100–750 mg and maintained with nitrous oxide in oxygen supplemented with either 0.5–1.5 % enflurane or 0.5–1.3 % isoflurane, as required. Neuromuscular blocking agents were used as required and, if necessary, residual block was antagonized with atropine 0.5–2.5 mg and neostigmine 0.5–5.0 mg. Analgesia was provided using fentanyl 25–800 μg during operation and morphine 2–120 mg after operation, as required.

All observations were made without knowledge of whether or not the patient had received active treatment or placebo. Nausea and vomiting were assessed by direct questioning of the patient at 1, 4 and 24 h after recovery from anaesthesia, defined as the first response to spoken command. Retching was not assessed separately. If patients experienced emetic sequelae, rescue antiemetic treatment was available. Patients who received rescue antiemetics were classed as treatment failures and considered to have experienced both nausea and vomiting.

Factors measured in these studies which were considered to have a possible effect on the proportion of patients experiencing postoperative nausea and vomiting were examined. Using a process of elimination based on logistic regression techniques, the most important factors and their interactions were isolated. A model including these factors was then used to calculate adjusted probabilities of postoperative nausea and vomiting for each category of factor included in the model, to give an impression of the pattern of frequencies of postoperative nausea and vomiting across the factors. The variables measured were: patient age, volatile anaesthetic (enflurane or isoflurane), dose of morphine given for postoperative analgesia (divided into three dose categories), total dose of fentanyl given for analgesia at induction and during maintenance of anaesthesia (divided into two dose categories), country, duration of anaesthesia, neuromuscular blocker (alcuronium, atracurium, vecuronium or pancuronium), antagonists of neuromuscular block (neostigmine, other or none), premedication (diazepam or temazepam), time to recovery, type of surgery (vaginal hysterectomy, abdominal hysterectomy or laparotomy), antiemetic treatment (ondansetron 1, 8 or 16 mg, or placebo) and body weight. The influence of each of the three individual trials was not included, as the studies were carried out in different countries and therefore the effects attributable to trial and to country could not be separated.

Initially, logistic models of the proportions of patients experiencing postoperative nausea and vomiting containing all the above factors were fitted. A χ^2 value for the overall fit of each model was obtained, together with the associated degrees of freedom. Further models were fitted, each excluding one factor. The difference between the χ^2 value obtained from the model including all factors and that obtained from the model excluding a particular factor gave a measure of the importance of that factor in explaining the observed proportion of postoperative nausea or vomiting. The rank order of the resulting significance levels gave an indication of the order of importance of the factors.

Factors found to be important influences on both postoperative nausea and vomiting were included in all further models. Initially, these factors were fitted alone and a χ^2 value for the model fit and the associated degrees of freedom obtained. Further models were fitted, each adding one of the remaining factors. The difference between the χ^2 value obtained from the model including the original factors and that obtained from the model adding one particular factor gave a measure of the added importance of that factor in explaining the observed proportion of postoperative nausea or vomiting. Use of the rank order of the resulting significance levels gave an indication of the order of importance of the remaining factors.

Further examination of the effect of the above factors on the proportion of patients experiencing postoperative nausea and vomiting was undertaken using a stepwise fitting procedure. The levels of significance required of a variable for entry to and exit from the model were fixed at 10 % beforehand, then variables were sequentially entered or removed from the model until no further variables met the required criterion for entry or exit. The variables included in the models obtained gave another indication of which factors were important influences on the proportions of postoperative nausea and vomiting.

When the important factors had been identified, two-way interactions between each pair of factors were investigated, using a method similar to that used to identify the important factors: initially a model containing just the factors was fitted, then further models, each including one two-way interaction. χ^2 tests were again used to identify any important interactions. Higher level interactions were not investigated because of the large number of variables required.

All analyses were performed on an Olivetti M380 using PC SAS version 6.04.

RESULTS

A total of 1257 patients were evaluated for frequency of postoperative nausea and vomiting and all the factors included in this analysis. Four hundred and twenty received placebo and 212, 296 and 329 received ondansetron 1, 8 and 16 mg, respectively.

Differences in the χ^2 value obtained from the overall model and those obtained from models excluding each factor individually are presented in table I, for both vomiting and nausea. A significance level of $P < 0.10$ was used to identify the most important factors. For vomiting these were (in order of increasing significance): antiemetic treatment, type of surgery, country, neuromuscular blocker and age. For nausea, the factors were antiemetic treatment, type of surgery, volatile anaesthetic and neuromuscular blocker. The three factors which were considered important for both vomiting and nausea (antiemetic treatment, type of surgery and neuromuscular blocker) were then included in all further models.

Using a basic model including these three factors, further models were fitted, each including one of the remaining factors. The χ^2 values, degrees of freedom and significance levels from this investigation are presented in table II, for both vomiting and nausea. This table shows that country and premedicant were important factors for both nausea and vomiting. Because premedicant had not seemed very important initially, the relationship between premedicant and other factors was investigated. It was found that all patients from four countries (Belgium, Denmark, France and Norway) and the majority of patients from two other countries (the Netherlands and Germany) received diazepam, whilst the majority of patients in the U.K. received temazepam. The effects of premedicant and country were therefore difficult to separate, and premedicant was excluded from further investigation.

TABLE I. *Effect of excluding individual factors*

			Change from overall model		
	χ^2	df	χ^2	df	P
Vomiting					
All variables	102.834	24			
Excluding					
Antiemetic treatment	41.317	21	61.517	3	< 0.001
Type of surgery	94.374	22	8.460	2	0.015
Country	88.016	18	14.818	6	0.022
Neuromuscular blocker	95.225	21	7.609	3	0.055
Age	99.847	23	2.987	1	0.084
Time to recovery	100.516	23	2.318	1	0.128
Premedicant	101.556	23	1.278	1	0.258
Weight	102.438	23	0.396	1	0.529
Dose of fentanyl	102.582	23	0.252	1	0.616
Dose of morphine	102.197	22	0.637	2	0.727
Volatile anaesthetic	102.715	23	0.119	1	0.730
NMB antagonist	102.793	23	0.041	1	0.840
Duration of anaesthesia	102.828	23	0.006	1	0.938
Nausea					
All variables	103.421	24			
Excluding					
Antiemetic treatment	58.981	21	44.440	3	< 0.001
Type of surgery	91.282	22	12.139	2	0.002
Volatile anaesthetic	99.740	23	3.681	1	0.055
Neuromuscular blocker	96.492	21	6.929	3	0.074
Country	93.327	18	10.094	6	0.121
NMB antagonist	102.007	23	1.414	1	0.234
Dose of morphine	101.113	22	2.308	2	0.315
Weight	103.076	23	0.345	1	0.557
Age	103.364	23	0.057	1	0.811
Time to recovery	103.388	23	0.033	1	0.856
Dose of fentanyl	103.411	23	0.010	1	0.920
Premedicant	103.418	23	0.003	1	0.956
Duration of anaesthesia	103.420	23	0.001	1	0.975

TABLE II. *Effect of including extra factors into basic model*

			Change from basic model		
	χ^2	df	χ^2	df	P
Vomiting					
Antiemetic treatment, type of surgery and neuromuscular blocker	76.206	8			
Including					
Country	94.169	14	17.963	6	0.006
NMB antagonist	80.014	9	3.808	1	0.051
Premedicant	79.565	9	3.359	1	0.067
Duration of anaesthesia	78.903	9	2.697	1	0.101
Age	78.035	9	1.829	1	0.176
Volatile anaesthetic	77.807	9	1.601	1	0.206
Dose of morphine	78.974	10	2.768	2	0.251
Dose of fentanyl	76.936	9	0.730	1	0.393
Weight	76.928	9	0.722	1	0.395
Time to recovery	76.321	9	0.115	1	0.735
Nausea					
Antiemetic treatment, type of surgery and neuromuscular blocker	73.410	8			
Including					
Premedicant	89.487	9	16.077	1	< 0.001
Country	94.677	14	21.267	6	0.002
Dose of morphine	83.020	10	9.610	2	0.008
Duration of anaesthesia	77.606	9	4.196	1	0.041
Dose of fentanyl	76.744	9	3.334	1	0.068
NMB antagonist	74.738	9	1.328	1	0.249
Age	73.690	9	0.280	1	0.597
Volatile anaesthetic	73.643	9	0.233	1	0.629
Weight	73.605	9	0.195	1	0.659
Time to recovery	73.469	9	0.059	1	0.808

Stepwise fitting was applied after constraining the model to include antiemetic treatment, type of surgery, neuromuscular block and country. The extra factors included in the final models were age for vomiting and volatile anaesthetic for nausea, which agreed with the factors identified in the initial elimination (table I). The model then used for investigation of interactions included antiemetic treatment, type of surgery, neuromuscular blocker, volatile anaesthetic and age.

A model including the factors identified as important using the above elimination procedures was fitted, and the χ^2 values and degrees of freedom obtained. Further models, each including one two-way interaction between a pair of factors were fitted. The difference in the χ^2 values obtained between the original model and a model including an interaction

TABLE III. *Adjusted probabilities of nausea and vomiting by treatment group*

Treatment group	n	Nausea	Vomiting
Placebo	420	0.75	0.61
Ondansetron 1 mg	212	0.71	0.54
Ondansetron 8 mg	296	0.54	0.34
Ondansetron 16 mg	329	0.57	0.39

TABLE IV. *Adjusted probabilities of nausea and vomiting by country*

Country	n	Nausea	Vomiting
United Kingdom	587	0.75	0.54
The Netherlands	231	0.61	0.52
France	76	0.57	0.40
Denmark	56	0.54	0.49
Belgium	46	0.53	0.37
Norway	125	0.51	0.37
Germany	136	0.49	0.34

TABLE V. *Adjusted probabilities of nausea and vomiting by neuromuscular blocker and by volatile anaesthetic*

	n	Nausea	Vomiting
Neuromuscular blocker			
Alcuronium	115	0.59	0.38
Atracurium	181	0.59	0.47
Vecuronium	685	0.63	0.46
Pancuronium	276	0.74	0.57
Volatile anaesthetic			
Enflurane	681	0.62	0.48
Isoflurane	576	0.69	0.49

TABLE VI. *Adjusted probabilities of nausea and vomiting by type of surgery and age group*

	Age category (yr)					
Type of surgery	< 40	n	≥ 40–< 50	n	≥ 50	n
Nausea						
Abdominal hysterectomy	0.66	233	0.68	431	0.72	157
Vaginal hysterectomy	0.72	44	0.67	67	0.61	61
Laparotomy	0.51	180	0.56	56	0.56	28
Vomiting						
Abdominal hysterectomy	0.46	233	0.49	431	0.54	157
Vaginal hysterectomy	0.58	44	0.65	67	0.54	61
Laparotomy	0.35	180	0.43	56	0.64	28

term provide a test for the statistical significance of the interaction. The only interaction found to be statistically significant for vomiting was type of surgery by age ($P = 0.016$). Whilst no interactions were significant at the 5 % level for nausea, the type of surgery by age interaction approached statistical significance ($P = 0.073$). This interaction was therefore included in the final model.

The factors found to be important influences on the frequency of postoperative nausea and vomiting were thus antiemetic treatment, neuromuscular blocker, country, volatile anaesthetic, type of surgery and age, the last two factors showing a statistically significant interaction. Adjusted probabilities of nausea and vomiting were obtained from this model.

For adjusted probabilities of nausea and vomiting in each treatment group (table III), the ondansetron 8 mg group showed the smallest adjusted probability of nausea and of vomiting, and the placebo treatment group the greatest. For adjusted probabilities of experiencing nausea and vomiting in different countries (table IV), the greatest probabilities occurred in the U.K. and the Netherlands. The rank order of countries by adjusted probability of postoperative nausea was similar to that seen for vomiting. The adjusted probability of nausea was greater than that for vomiting in each of the countries included. For neuromuscular blockers, the adjusted probabilities of nausea and vomiting were both smallest in the alcuronium group and greatest in the pancuronium group (table V). Adjusted probabilities were slightly greater when anaesthesia had been maintained using isoflurane compared with enflurane (table V).

The effects of age and type of surgery were found to have a statistically significant interaction, hence the individual effects of these factors could not be assessed in the study population as a whole. For display purposes, the continuous age variable has been grouped into three age categories. The adjusted probabilities of nausea and vomiting appeared to increase with increasing age for the abdominal

hysterectomy type, for either nausea or vomiting (table VI). The observed interaction between age and type of surgery for vomiting may be explained in part by a very high adjusted probability of vomiting in patients who were aged 50 yr or more and had undergone laparotomy.

DISCUSSION

The combination of data obtained from these three large, international studies has allowed evaluation of several factors considered to influence the frequencies of postoperative nausea and vomiting. The statistical model developed indicates those factors having a more important influence. Whilst some indication of their relative importance was obtained, no direct statistical comparison of the levels of each factor was performed. The model obtained confirms the multifactorial nature of the occurrence of postoperative nausea and vomiting and illustrates the possibility of interactions between the different influences; it may be used to support or challenge published findings concerning influences in this area.

Postoperative nausea and vomiting are amongst the most common symptoms reported after surgery and the adjusted probabilities of experiencing nausea and vomiting in the placebo group (0.75 and 0.61, respectively) are not dissimilar to incidences reported previously after major gynaecological surgery [3–5].

Currently, little information is available on the variation in the frequencies of postoperative nausea

[redacted]

are rarely seen in some countries, it would appear that there are significant problems in all the countries included in the present study, although the symptoms may be encountered slightly less frequently in some countries than in others. The reasons for these variations are unclear at present, but may represent subtle variations in anaesthetic practice or postoperative care not accounted for in the present study.

The probabilities of experiencing postoperative nausea and vomiting are generally believed to decrease with increasing age of the patient [1, 2]. Indeed, it has been shown that children are more likely to vomit after operation than adults [6]. However, the influence of age may not be as clear when an adult population is studied. The interaction between age and type of surgery found in this study prevented isolation of the influence of age alone. However, it appeared that the adjusted probabilities of nausea and vomiting increased with increasing age for abdominal hysterectomy and laparotomy. Similarly, the influence of type of surgery alone could not be isolated, although laparotomy appeared to result in generally smaller probabilities of postoperative nausea and vomiting than abdominal or vaginal hysterectomy. A lack of clear effect of age on nausea and vomiting has been observed previously by Knapp and Beecher [7], who were unable to detect any effects of age on postoperative nausea and vomiting. More recently, van den Berg, Lambourne and Clyburn were unable to demonstrate an effect of age on postoperative vomiting after ophthalmic surgery [8].

Maintenance of anaesthesia with enflurane resulted in slightly smaller adjusted probabilities of experiencing nausea and vomiting than did maintenance with isoflurane. These differences are probably of little clinical significance. In the few studies in which comparison of the incidence of postoperative nausea and vomiting has been made after anaesthesia with halothane, enflurane and isoflurane, no significant difference between the agents was observed [9].

The type of neuromuscular blocker used appeared to influence the probability of experiencing nausea and vomiting, patients who received pancuronium being most likely to suffer nausea or to vomit. The reasons why varying proportions of patients should experience nausea and vomiting after different myoneural blockers are unclear. However, a possible explanation for patients having a greater probability of nausea and vomiting after receiving pancuronium may be its sympathomimetic activity. A greater incidence of nausea and vomiting is observed with drugs which are known to release endogeneous catecholamines [10]. Pancuronium, unlike other non-depolarizing neuromuscular blockers, releases noradrenaline, which may be an additional influencing factor [11].

Use of neostigmine to antagonize neuromuscular block has previously been reported to result in an increased frequency of postoperative nausea and vomiting [12], although this finding was not supported in the present study. The reason for this discrepancy is unclear, although King and colleagues [12] performed their study in 38 patients who were undergoing orthopaedic surgery, while the present study was performed in a much larger population who underwent gynaecological surgery.

Body weight has been reported to influence the frequencies of postoperative nausea and vomiting [1, 2]. McKenzie and colleagues [13] found increasing frequencies of nausea, retching and vomiting with increasing body weight in patients receiving general anaesthesia for therapeutic abortion. In the present study, however, we were unable to detect any influence of body weight. This may have been caused by the fact that restrictions were placed on the entry criteria which excluded patients weighing less than 45 kg or more than 90 kg.

The duration of anaesthesia has often been linked with postoperative nausea and vomiting [1, 2], with patients considered to be more likely to vomit after operations of longer duration [14]. There did not appear to be any influences caused by the duration of anaesthesia in the present study (median 90 (interquartile range 65–120) min). The lack of effect may be explained by the fact that only a limited number of surgical procedures was included. Interestingly, Karlsson, Larsson and Nilsson [15] were unable to demonstrate an increase in the frequency of postoperative nausea with increasing duration of anaesthesia in a study of paediatric patients in whom anaesthesia was maintained with halothane.

The present study has described the development of a statistical model for evaluating the importance of factors considered to influence the incidence of postoperative nausea and vomiting. In the population studied, this process has highlighted a number of factors such as duration of anaesthesia and body weight which may not be as important as originally thought. Further controlled studies using similar statistical techniques can help to confirm the findings from this study and establish which of the various influences may be clinically of most importance. Other factors such as previous history of postoperative nausea and vomiting, preoperative anxiety, pain, ambulation and timing of oral intake, which were not included in the current investigation, could be the subject of future research.

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POWER SPECTRAL ANALYSIS OF HEART RATE VARIABILITY AFTER SPINAL ANAESTHESIA

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SUMMARY

Power spectral analysis of heart rate (HR) variability is a useful tool with which to assess cardiac autonomic activity. The low frequency bands have been considered as both sympathetically and parasympathetically mediated components, while the high frequency bands have been assumed to be the parasympathetically mediated respiratory components. It has been anticipated that spinal anaesthesia to the thoracic level may modulate cardiac autonomic activity to reduce HR and arterial pressure by blocking cardiac sympathetic activity. In order to quantify the alterations in cardiac autonomic activity, we have analysed the power spectra of HR variability for 30 min after subarachnoid administration of hyperbaric amethocaine. Using 256-s R–R interval data obtained from continuously recorded ECG, low frequency (Lo: 0.04–0.15 Hz) and high frequency (Hi: 0.15–0.40 Hz) band widths were integrated and their serial alterations were computed by shifting subjected R–R intervals at 60-s intervals. After the subarachnoid injection, arterial pressure, HR and Lo decreased and Hi and the Hi:Lo ratio increased. These changes were observed within 15–20 min. Ventilatory frequency did not change throughout the study. These findings suggest that the decrease in HR and arterial pressure after subarachnoid administration of hyperbaric amethocaine reflect decreased sympathetic activity and increased parasympathetic activity in the cardiac autonomic nervous system. (Br. J. Anaesth. 1993; **71**: 523–527)

KEY WORDS

Anaesthetic techniques: spinal. Monitoring: heart rate variability. Measurement technique: power spectral analysis.

Bradycardia associated with spinal anaesthesia occurs commonly when a high level of block is produced. Both unopposed parasympathetic activity and reduced sympathetic tone are thought to be the causes [1]; of the two neurogenic mechanisms, increased parasympathetic activity is considered more important [1, 2]. However, the respective sympathetic and parasympathetic contributions have not been quantified clearly, because no effective monitor is available during anaesthesia.

The cardiac autonomic nervous system plays a vital role in neural control for maintaining cardiovascular stability. To elucidate its contribution to cardiac sinus rhythm, we have used power spectral analysis of heart rate (HR) variability to study the physiological and pathophysiological properties of the system [3–5]. Two spectral components of HR variability have been observed in dogs and humans: a low frequency component, considered to be of vasomotor origin mediated by the parasympathetic and sympathetic systems, and a high frequency component, centered at the frequency of ventilation mediated primarily by the parasympathetic system. A decreased high frequency component during isoflurane anaesthesia has been reported [6] and shown to be dose related [7]. However, no study has been carried out during regional block including spinal anaesthesia.

The purpose of this study was to examine the effect of hyperbaric spinal anaesthesia on the cardiac autonomic nervous system using successive power spectral analyses of HR variability, calculated from the digitized R–R intervals from taped ECG.

PATIENTS AND METHODS

We studied 26 ASA class I and II patients having elective lower abdominal or limb surgery under spinal anaesthesia. After approval by the local Research Review Board, informed consent was obtained from all participants. Patients with a history of cardiovascular disease, arrhythmia or cardiac autonomic nervous system diseases such as diabetes mellitus were excluded from the study. No patient was receiving concurrent medication.

Each patient received midazolam 0.1 mg kg^{-1} 1 h before induction of anaesthesia. Atropine was not given. On arrival in the operating room, patients were placed in the supine position and routine monitors including pulse oximetry, ECG (lead II), impedance respiratory signals and automated sphygmomanometry were started (BSM-8500, Nihon Kohden, Tokyo, Japan). An i.v. cannula was inserted and 6% hydroxyethylated starch in saline admin-

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istered at a rate of 10 ml kg^{-1} h^{-1} for 30 min, followed by Hartmann's solution 10 ml kg^{-1} h^{-1}. With the patient in the left lateral position, the extradural space was located at L1–2 with a 17-gauge needle and a catheter was placed cephalad. A 25-gauge spinal needle was inserted at L2–3 and a small dose of hyperbaric 0.5% plain amethocaine in 10% glucose was injected at a rate of 0.2 ml s^{-1} without barbotage. No injection was made through the catheter at this time.

Timing commenced from the start of the spinal injection. The patient was then returned to the supine position. Baseline variables were measured before spinal injection in the supine position and at 5, 10, 15, 20, 25 and 30 min after spinal injection. Consecutive recordings of impedance respiratory signals and ECG were made onto magnetic tape for 256 s at baseline and for 30 min during the study. The dermal level of anaesthesia was determined by absence of sensation to pinprick in the mid axillary line bilaterally at 5, 10, 15, 20, 25 and 30 min. Surgery proceeded when an adequate block was achieved more than 30 min after spinal injection. Routine management of the patient was not affected by their inclusion in the study; patients who required ephedrine 4–8 mg to treat hypotension ($\leqslant$ 80 mm Hg systolic) or atropine 0.25–0.5 mg for bradycardia ($\leqslant$ 50 beat min^{-1}) were excluded from the study, as these vasoactive agents modify the power spectrum. No patient was placed in the Trendelenburg position. All were kept awake and supine during the study. If spinal anaesthesia was thought insufficient at 30 min, extradural anaesthesia was commenced.

Data analysis

Mean arterial pressure (MAP) was calculated as:

$$\text{MAP} = [(\text{systolic pressure}) + 2 \times (\text{diastolic pressure})] \div 3$$

The monitor was equipped with a high-cut filter above 5 Hz for impedance respiratory signals and a drift-free filter for the ECG channel. Ventilatory frequency (f) was determined from impedance respiratory signals.

The ECG channel was recorded onto magnetic tape (RD-111T, TEAC, Tokyo, Japan) and digitized at 500 Hz for off-line analysis. ECG was recorded with care to avoid artefacts such as muscle contractions and electrical noise. The computer program processed the digitized data using a 14-bit A–D converter-equipped desk-top computer system (PC98, NEC, Tokyo, Japan) and detected QRS complexes and R waves. The program measured the time difference between two R waves to obtain an R–R interval tachogram (fig. 1A, B) [8, 9]. Instantaneous HR data from 256-s R–R interval segments were converted to 1/R–R interval length by sampling at 4 Hz and the 256-s segment of R–R intervals was subjected to off-line spectral analysis because the raw R–R data were inappropriate for fast Fourier transform analysis. For fast Fourier transform-based power spectral analysis, a rectangular local window periodogram method was used as a low-pass anti-aliasing digital filter beyond the Nyquist sampling rate (2 Hz), which enabled computation of reliable spectral estimates between 0 and 1 Hz [8, 9]. The power spectra at frequencies less than 0.5 Hz were standardized as the square of the mean of HR (Hz^{-1}) (fig. 1C) [8, 9].

At every 60-s interval, the analysis was repeated on successive records of R–R interval data; by overlapping the R–R interval data of 196 s duration, the power spectral analysis was carried repeatedly using the next incoming 60-s segment of R–R interval data (fig. 1B). Spectral accuracy was confirmed by testing a sequence of simulated R–R intervals generated by an integral pulse frequency modulation model [9]. The spectra were quantified by determining the areas of the spectrum in two components: low frequency (Lo: 0.04–0.15 Hz) and high frequency (Hi: 0.15–0.40 Hz) band areas. The peak areas of the power spectral densities were integrated and the Hi:Lo ratio computed [3, 10]. Log power of these peak areas and the Hi:Lo ratio were calculated by taking their common logarithms (base 10) from confirmed normal distributions [5, 8, 11, 12].

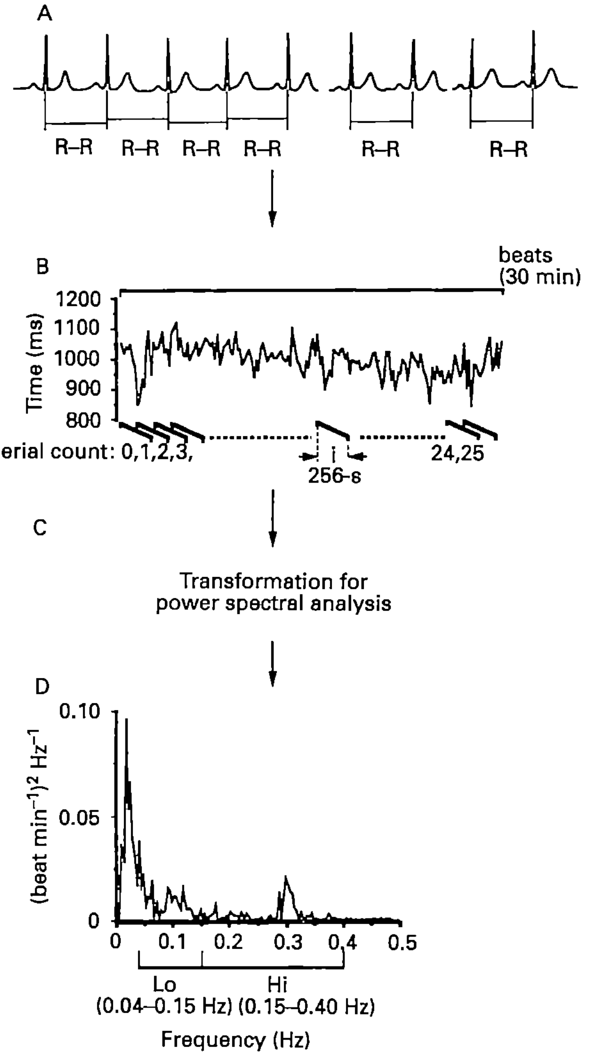

FIG. 1. Method of power spectrum analysis from stored R–R interval tachograms obtained from continuously recorded ECG. A: Recorded ECG. B: R–R interval tachogram. C: Each 256-s R–R interval is transformed into 1024 instantaneous heart rate for power spectral analysis based on fast Fourier transform. D: A power spectrum from 256-s interval data.

TABLE I. *Changes in time-related variables (mean* (SD) *or median (range)).* f = *Ventilatory frequency.* *P < *0.05;* **P < *0.01 compared with baseline using ANOVA followed by Scheffé's test. No significant differences between left and right side levels of anaesthesia*

	Baseline	5 min	10 min	15 min	20 min	25 min	30 min
f (b.p.m.)	15.9 (3.0)	14.9 (3.9)	15.1 (2.9)	15.7 (3.9)	16.4 (3.6)	16.2 (3.6)	16.2 (4.7)
MAP (mm Hg)	83 (14)	77 (10)*	76 (10)**	75 (10)**	75 (10)**	75 (9)**	75 (9)**
R–R interval							
Mean (ms)	767 (123)	779 (127)	824 (134)	847 (125)*	849 (127)*	850 (124)*	853 (122)*
Variance (ms^2)	1783 (1186)	2037 (1484)	2232 (1601)	1933 (1299)	2071 (1284)	2054 (1302)	2033 (1478)
Level of anaesthesia							
Left side	—	T7 (T4–T11)	T5 (T3–T10)	T4 (T2–T8)	T4 (T2–T6)	T4 (T2–T5)	T4 (T2–T5)
Right side	—	T7 (T4–T11)	T5 (T3–T10)	T4 (T2–T9)	T4 (T2–T5)	T4 (T2–T5)	T4 (T2–T5)

Data of normal distribution are presented as mean (SD). From segments of R–R interval tachograms at each sampling time, simple statistics (mean and variance) were calculated. HR was calculated from the reciprocal of R–R interval. Variations in ventilatory frequency, MAP, R–R interval and R–R variance were compared using one-way analysis of variance (ANOVA) for repeated measurements, followed by Scheffé's test. Variations in log power and HR calculated from R–R interval tachograms were compared repeatedly using ANOVA, followed by Fisher's protected least significant difference test. The thoracic dermal level of anaesthesia was recorded as median (range) and compared using Wilcoxon matched pairs signed rank test for paired comparisons (right *vs* left side), as a normal distribution could not be assumed. Comparisons between the median level of anaesthesia and mean log Hi:Lo used linear regression analysis and Kendall's rank correlation. $P < 0.05$ was considered statistically significant.

RESULTS

No serious complications including hypoxaemia were observed in any of the 26 participants. However, six patients were excluded from the study as they received ephedrine ($n = 3$), atropine ($n = 1$) and both ephedrine and atropine ($n = 2$) within 30 min of the spinal injection. Subjects for the study thus consisted of 20 patients (13 female) aged 21–56 yr (mean 36 yr). The mean dose of hyperbaric amethocaine solution was 1.80 (0.14) ml (range 1.6–2.0 ml). No patient required extradural analgesia at 30 min. The extradural catheter was removed the day after surgery, and there was no damage to the catheter by the spinal needle.

Ventilatory frequency did not change throughout the study (table I). MAP began to decrease at 5 min ($P < 0.05$) and remained decreased ($P < 0.01$) thereafter. Mean R–R interval increased at 15 min ($P < 0.05$) and remained increased thereafter ($P < 0.01$), although R–R variance did not change during the study. The highest dermal level of anaesthesia was reached within 15 min on both sides. HR increased transiently just after the spinal injection ($P < 0.05$), began to decrease after 8 min ($P < 0.05$) and remained less than baseline thereafter ($P < 0.01$) (fig. 2). Log Lo decreased after 6 min ($P < 0.05$) and remained less than baseline thereafter ($P < 0.01$). Log Hi and log Hi:Lo increased after 3 and 4 min ($P < 0.05$), respectively, and remained greater than baseline throughout the study ($P < 0.01$). The increase in log Hi:Lo was significantly dependent on the dermal level of anaesthesia (Kendall's rank correlation: $r^2 = 0.98$ and $P = 0.04$) (table I, fig. 3).

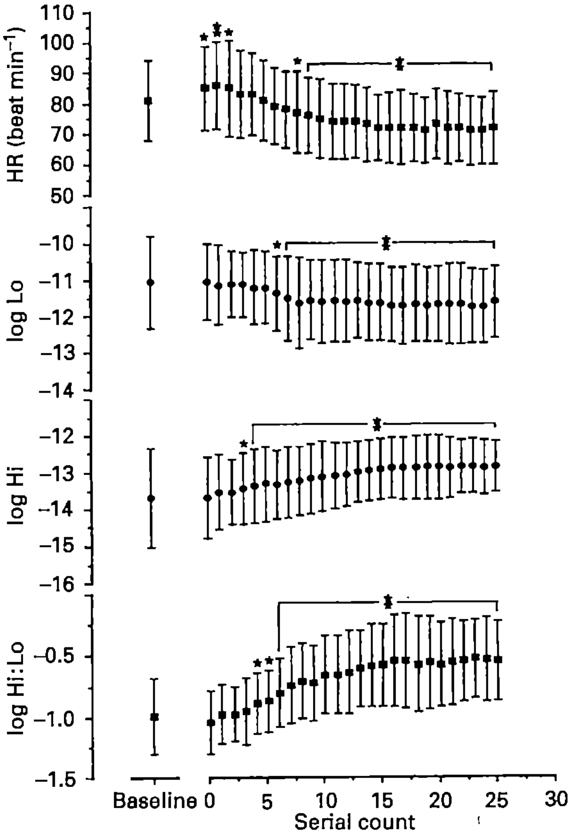

FIG. 2. Serial changes in heart rate (HR), high frequency peak area (Hi), low frequency peak area (Lo) and Hi:Lo ratio (mean, SD). Serial count indicates starting time of recordings of 256-s R–R interval segments. *$P < 0.05$; **$P < 0.01$ compared with baseline.

DISCUSSION

We demonstrated that spinal anaesthesia with hyperbaric amethocaine not only decreased cardiac sympathetic activity but also increased parasympathetic tone. These effects were time-dependent and related to the level of spinal anaesthesia, the cardiac autonomic nervous system becoming more vagotonic as the dermal level moved cephalad.

Neural regulation of HR variability has been assessed with power spectral analysis based on fast Fourier transform [3], when two major components are usually recognized at about 0.1 Hz and 0.3 Hz in

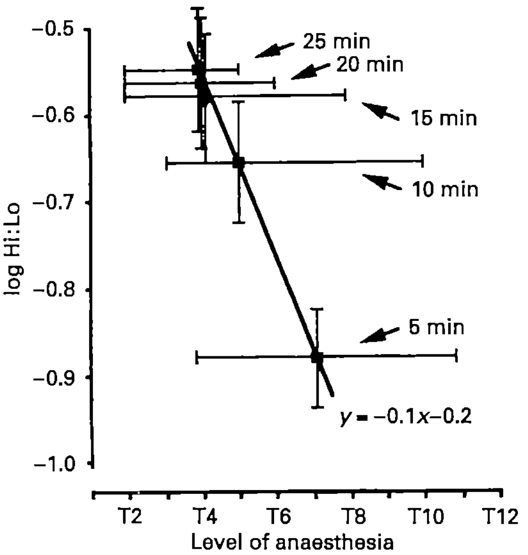

FIG. 3. Linear relationship between median of thoracic dermal level of anaesthesia and mean of log Hi:Lo, obtained at 5, 10, 15, 20 and 25 min after spinal injection (arrow). Vertical bars represent mean, SEM ($n = 20$). Horizontal bars represent median (range), derived from the observation of right and left side level of anaesthesia at every sampling time. Linear regression ($r^2 = 0.98$) and Kendall's rank correlation coefficient were both significant ($P < 0.05$).

the range < 0.5 Hz. The former is considered to reflect the sympathetically and parasympathetically mediated outflows and the latter (respiratory sinus arrhythmia) to reflect parasympathetic vagal efferent activity [3, 5, 13]. Lo reflects both sympathetic and parasympathetic input to the heart, because pharmacological blocking studies suggest that parasympathetic reflexes are involved [12]. Hi primarily represents the variation caused by respiratory sinus arrhythmia. The Hi:Lo ratio is thus considered a convenient index of the interaction of the two neural systems [3, 8, 14].

The band width for integration varies between reports, as it has been analysed by different methods [3, 5, 8, 10, 14, 15]. The oscillations about a frequency of 0.1–0.25 Hz comprise the main component of information on neural modulation of the sinoatrial node [12]. Oscillations with a frequency < 0.03 Hz cannot be described accurately, hence those components between 0 and 0.03 Hz are considered to be d.c. noise [3, 12]. The clearest sympathetic component is that which centres around 0.1 Hz; consequently, we analysed our data with the window for Lo set at 0.04–0.15 Hz. Some reports subdivide Lo into two components: very low frequency (0.04–0.10 Hz) and a mid-frequency band (0.10–0.15 Hz) [16]. The latter component may be related to the frequency response of the baroreceptor reflex, which was not investigated in this study. The high frequency component (Hi: 0.15–0.4 Hz) is reported as being proportional to tidal volume and inversely proportional to ventilatory frequency [13, 17]. As Hi disappears after atropine, it may also represent a clinically useful index of vagal activity [14]. Our integration was determined between the band widths to exclude high frequency noise > 0.4 Hz.

Isoflurane anaesthesia depresses total power, including both low and high frequency components in the power spectrum, and the depression of the central nervous system and the cardiac autonomic nervous system may be involved in this mechanism [6, 7]. However, the results observed in this study may reflect a different mechanism. Time-dependent sympathetic cephalad block might mainly reduce sympathetic activity, as the preganglionic sympathetic cardiac accelerator fibres leaving the spinal cord at T1–4 are easily blocked at higher levels of spinal anaesthesia. Cardiac autonomic nervous system activity is known to be depressed by spinal analgesia, as sympathetic block may extend two to six dermal segments higher than sensory loss [1, 18]. Our dermal level of sympathetic block may have been sufficiently higher than T1–2 to block cardiac accelerator fibres.

It was not clear why spinal analgesia increased parasympathetic activity as shown in this study. We presumed two major reasons: ventilation-mediated enhancement of parasympathetic activity and parasympathetic reflex mechanisms in the heart. Ventilation mediates parasympathetic activity via the vasomotor centre and modulates cardiac sinus node activity: it can influence both Lo and Hi [17]. As shown in our study, ventilatory frequency appears not to play an important role in this mechanism, although tidal volume was not measured.

Within 20 min after the spinal injection, Lo and Hi seemed to have reached their maximal upper dermal level. Simultaneous alterations in HR and MAP were also observed with changes in Lo and Hi. These findings suggest that spinal anaesthesia affects both sympathetic and parasympathetic activity to make the cardiac autonomic nervous system vagotonic.

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LACK OF A CEILING EFFECT FOR INTRATHECAL BUPRENORPHINE ON C FIBRE MEDIATED SOMATOSYMPATHETIC REFLEXES

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SUMMARY

We observed that buprenorphine 20 μg kg^{-1} i.v. in dogs caused an initial significant reduction in both Aδ and C fibre mediated somatosympathetic reflexes evoked by tibial and radial nerve stimulation, to approximately 75% and 70% of control values. Larger doses (up to 100 μg kg^{-1} i.v.) had progressively less effect and the mean responses were depressed to only approximately 65% and 55% of control, indicating a ceiling effect. Buprenorphine 450 μg intrathecally (i.t.) completely abolished tibial C fibre reflexes, but 20% of Aδ responses could not be eliminated with doses up to 1050 μg i.t. Fentanyl 100 μg kg^{-1} i.v. or 150 μg i.t. after buprenorphine i.v. or i.t., respectively, had little additional effect. This study confirms the limited ceiling effect of buprenorphine on nociceptive reflexes when administered systemically, and provides evidence that when administered i.t. in sufficient doses it abolishes the C responses (lack of ceiling effect for C responses), but the Aδ responses show a plateau or ceiling effect. (Br. J. Anaesth. 1993; **71**: 528–533)

KEY WORDS

Anaesthetic techniques: spinal, intravenous. Analgesics: buprenorphine. Nerve: A fibres, C fibres. Reflexes: somatosympathetic.

Partial opioid agonist-antagonists, such as buprenorphine, are considered to have a bell-shaped dose–response curve in their actions,—that is, a ceiling effect [1], such that analgesia can be achieved without respiratory or cardiovascular depression. However, severe respiratory depression and apnoea have been reported after administration of buprenorphine extradurally [2], sublingually [3] and i.m. [4], unresponsive to naloxone in doses of 0.2–1 mg i.v. [2, 3]. Thus it appears that there is no ceiling effect on respiratory depression. This is in disagreement with the concept of a ceiling effect, for example, for analgesia as suggested previously [1], although buprenorphine administered spinally has in general produced satisfactory analgesia, for example in postoperative patients [1]. Also, there was no sign of a ceiling effect during studies of analgesia using rat tail-flick and writhing tests [5]. However, such studies are often limited in the amount of pain which can be induced in a conscious animal while avoiding tissue damage. Thus it is uncertain if buprenorphine has a ceiling effect on nociception in the spinal cord and the effects of the drug may differ when it is administered via the intrathecal (i.t.) or i.v. routes.

This study was undertaken to provide more information on the potential selectivity or otherwise of the ceiling effect of buprenorphine, for example, on the somatosympathetic responses evoked by small myelinated group III (Aδ) and unmyelinated group IV (C) fibres in the somatic nerves. This would provide a possible explanation of unexpected clinical phenomena inappropriate for its putative pharmacological profile.

METHODS

Experiments were approved by the Home Office (Project Licence No. PPL 70/01654). Eight greyhound dogs (weight 25.2–29.7 kg) were anaesthetized with 1% methohexitone 15–20 mg kg^{-1} i.v. followed by 1% α-chloralose 30 mg kg^{-1} i.v. as a bolus and thereafter 17–20 mg kg^{-1} h^{-1} by infusion. The trachea was intubated and the dog paralysed with suxamethonium 10 mg kg^{-1} i.v. every 30 min; the lungs were ventilated mechanically with oxygen-enriched air. The femoral artery and vein were cannulated. pHa, Pa_{CO_2}, Pa_{O_2} and oesophageal temperature were maintained in the ranges 7.30–7.35, 4.5–5.5 kPa, 23–27 kPa, and 37–39 °C, respectively, throughout. Mean arterial pressure (MAP) measured using a strain gauge transducer, together with beat-by-beat heart rate (HR) obtained from ECG were recorded on a heated stylus system [Devices M19] throughout.

Surgical procedures

Intrathecal cannulae (22G Y-can, Wallace Ltd) were inserted through the dura which was exposed by lumbar laminectomy (L2–3). The renal sympathetic nerves were exposed retroperitoneally along

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the renal artery. A lateral superficial branch of the radial nerve in the left foreleg and a tibial nerve in the right hindleg were exposed. All nerves were dissected, cut distally and desheathed at the recording and stimulating sites.

Nerve stimulation and recording

All nerves were mounted on silver–silver chloride electrodes in a warm paraffin pool. Supramaximal electrical stimuli (0.33 Hz, 30 V and 0.5 ms) were applied to the radial and tibial nerves using a Grass S88 stimulator with matching direct-coupled isolation units (Grass 478A).

The evoked responses in renal sympathetic nerves have two components corresponding to activation of Aδ and C fibre pathways, respectively [6, 7]. The signals from the renal sympathetic nerves were processed through a preamplifier (Tektronix 122) and displayed on an oscilloscope (Tektronix 565). Groups of 16 evoked responses were averaged (Neurolog NL750), rectified and integrated (Neurolog NL703). Both rectified and integrated signals were recorded on a hot stylus recorder (Lectromed mulitrace 2). The integrated signals were displayed also on a Gould 1602 system which also measured the total averaged electrical activity in arbitrary units. On each occasion, two recordings of the averaged evoked responses were measured.

Drug administration

I.v. buprenorphine. A total dose of 100 μg kg^{-1} was administered by an infusion in four preparations. The initial rate of infusion was 2.5 μg kg^{-1} min^{-1} to a total dose of 30 μg kg^{-1} and thereafter 5 μg kg^{-1} min^{-1}. After total doses of 10 μg kg^{-1}, 20 μg kg^{-1}, 30 μg kg^{-1} and 50 μg kg^{-1}, the infusion was stopped and two averaged somatosympathetic reflexes were recorded which required approximately 5.0 min, after which the infusion was restarted. Fentanyl 100 μg kg^{-1} was injected i.v. as a bolus 15 min after total doses of buprenorphine of 100 μg kg^{-1}.

I.t. buprenorphine was also administered in another four preparations in incremental doses of 20 μg, 20 μg, 40 μg, 80 μg, 140 μg and 150 μg, each in 0.5 ml diluted when necessary with physiological saline solution (0.9 %), and finally 600 μg in 2 ml, at intervals of 10 min. Fifteen minutes after the last dose of buprenorphine, fentanyl 150 μg (3 ml) was administered i.t.

Fifteen minutes after the last dose of fentanyl, naloxone was administered i.v. in two doses each of 2 mg at 10 min intervals, in all preparations.

Analysis of variance and paired *t* tests, where appropriate, were used for statistical analysis.

RESULTS

I.v. buprenorphine

Tibial nerve stimulation. The Aδ and C fibre-mediated somatosympathetic responses were reduced significantly, to 75.4 % and 72.1 % of control values, respectively ($P < 0.05$), after buprenorphine 20 μg kg^{-1}. However, a much greater dose produced little additional effect and when the dose was increased to a total of 100 μg kg^{-1} the Aδ and C reflexes were depressed to only 67.5 % and 57.4 %, respectively, of control. There were no statistically significant differences between the effects of buprenorphine on the Aδ and C reflexes.

After buprenorphine, fentanyl 100 μg kg^{-1} i.v. produced only a small further depression of the Aδ reflexes, but had no effect on C reflexes (figs 1, 2), whereas in an opioid naïve preparation this dose of fentanyl would be expected to abolish both Aδ and C fibre-mediated somatosympathetic reflexes in an identical animal model [8].

Radial nerve stimulation. The effects of buprenorphine i.v., followed by fentanyl i.v., on the Aδ and C fibre-mediated somatosympathetic responses evoked by stimulation of the radial nerve were similar to its effect on tibial nerve responses.

I.t. buprenorphine

Tibial nerve stimulation. Both Aδ and C fibre-mediated somatosympathetic responses evoked by stimulation of the tibial nerve were depressed significantly, to approximately 65 % of control values ($P < 0.05$) after buprenorphine 80 μg. The Aδ and C reflexes were inhibited to approximately 55 % and 30 % of control, respectively, ($P < 0.05$) after total doses of buprenorphine 160 μg. Whereas the C reflexes were abolished completely after total doses of 450 μg, the Aδ reflexes were reduced on average to only 22.8 % of control ($P < 0.01$) and larger doses, even up to 1050 μg, produced no further effect on the Aδ responses, indicating a ceiling or plateau effect for the Aδ but not the C responses.

After buprenorphine i.t., fentanyl 150 μg i.t. produced no additional effect on Aδ reflexes (figs 2, 3) and this dose of fentanyl in the absence of buprenorphine would be expected to abolish this reflex [9].

Radial nerve stimulation. There were no statistically significant changes in the Aδ and C reflexes evoked by radial nerve stimulation throughout in the preparations receiving i.t. buprenorphine and fentanyl. Although both responses were reduced slightly after a total dose of 1050 μg, as a result of either systemic absorption or supraspinal spread, the reduction did not reach statistical significance (figs 2, 3).

Cardiovascular changes

The averaged MAP was reduced significantly, to 155 mm Hg and 145 mm Hg from the control value of 170 mm Hg after buprenorphine 50 and 100 μg kg^{-1} i.v., respectively. HR was also depressed significantly, to 125, 95, 85 and 80 beat min^{-1} from 140 beat min^{-1} after buprenorphine 20, 30, 50 and 100 μg kg^{-1} i.v., respectively. After buprenorphine, fentanyl 100 μg kg^{-1} i.v. reduced the mean MAP to

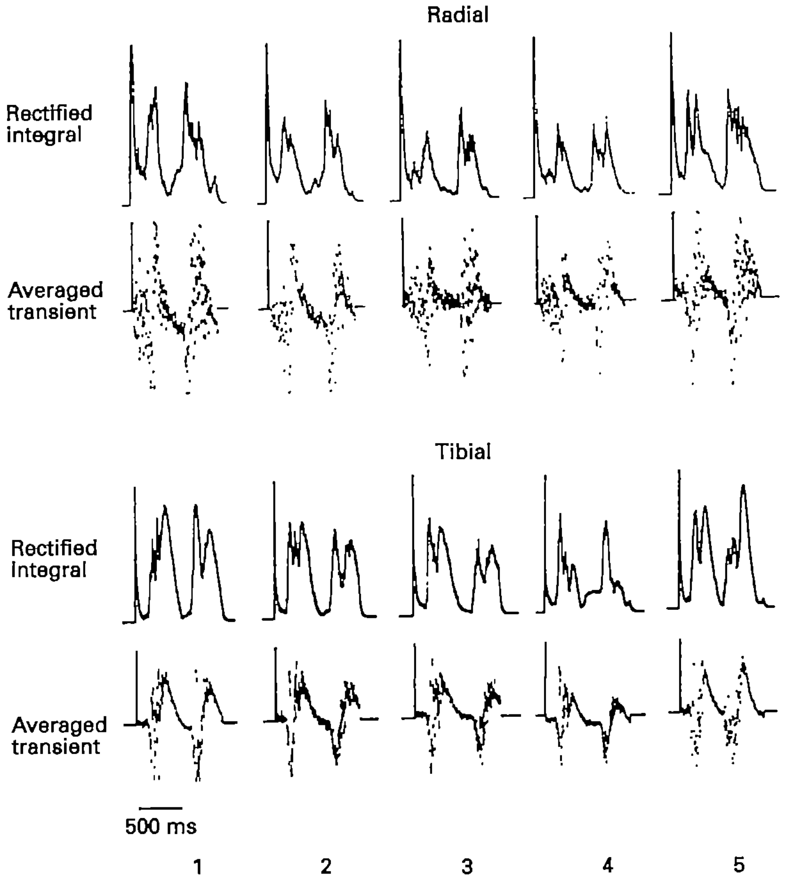

FIG. 1. Effects of i.v. buprenorphine followed by fentanyl and naloxone on Aδ (early response) and C (late response) fibre-mediated somatosympathetic reflexes, in a renal sympathetic nerve evoked by supramaximal electrical stimulation of the radial and tibial nerves (0.33 Hz, 30 V, 0.5 ms duration), in one representative preparation. Upper traces are the rectified integral of averaged signals and lower traces are averaged transients of 16 responses. Left to right: 1 = control; 2 = buprenorphine total doses of 20 μg kg^{-1} i.v.; 3 = buprenorphine total doses of 100 μg kg^{-1} i.v.; 4 = 5 min after fentanyl 100 μg kg^{-1} i.v.; 5 = 5 min after naloxone total dose 4 mg i.v.

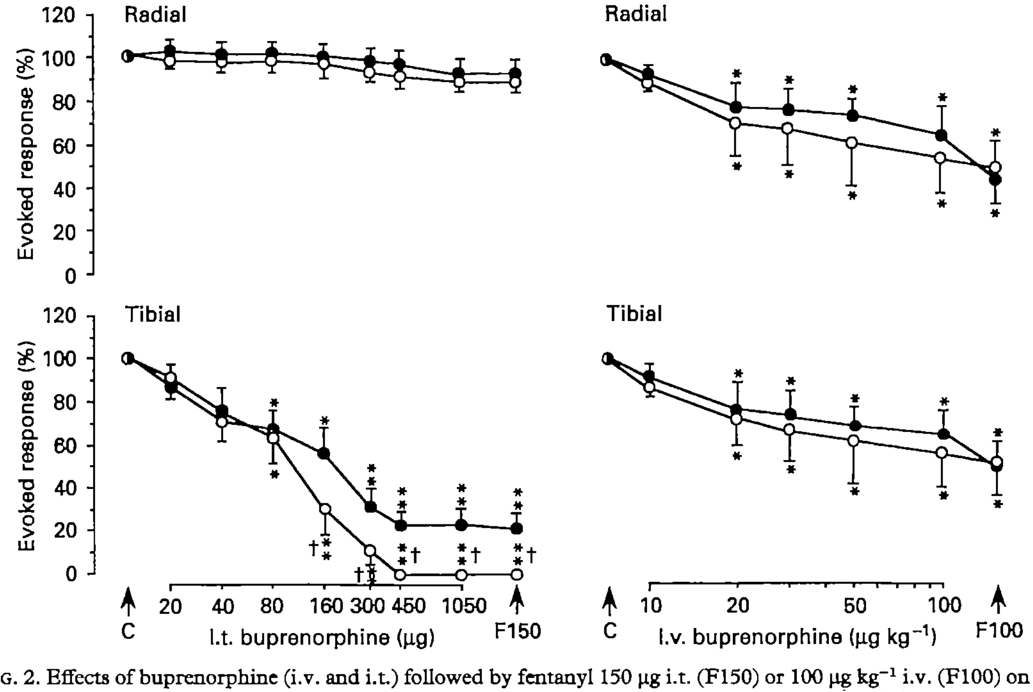

FIG. 2. Effects of buprenorphine (i.v. and i.t.) followed by fentanyl 150 μg i.t. (F150) or 100 μg kg^{-1} i.v. (F100) on the mean processed data (mean, SD as % of control; $n = 4$) of somatosympathetic reflexes evoked by supramaximal electrical stimulation of radial and tibial nerves. The dose of buprenorphine is shown on the logarithmic scale as the cumulative dose. ● = Response to Aδ fibres; ○ = response to C fibres. Aδ and C fibre-mediated responses relative to control: $^*P < 0.05$, $^{**}P < 0.01$; C reflexes compared with Aδ: $^{\dagger}P < 0.05$.

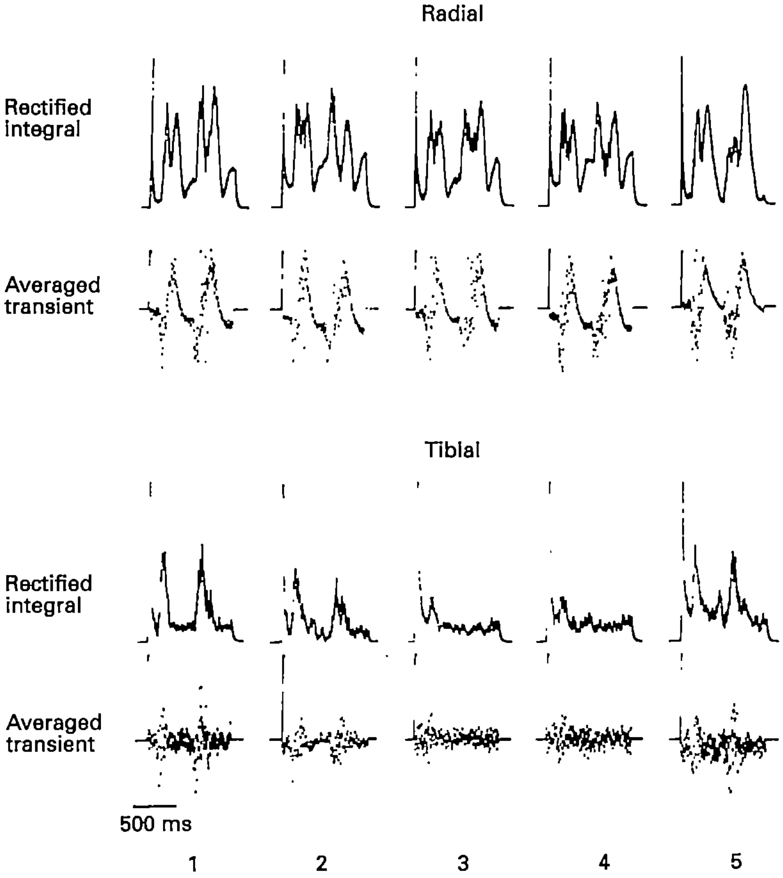

FIG. 3. Effects of i.t. buprenorphine followed by fentanyl and naloxone on Aδ (early response) and C (late response) fibre-mediated somatosympathetic reflexes, in a renal sympathetic nerve evoked by supramaximal electrical stimulation of the radial and tibial nerves (0.33 Hz, 30 V, 0.5 ms duration), in one representative preparation. Upper traces are the rectified integral of averaged signals and lower traces are averaged transients of 16 responses. Left to right: 1 = control; 2 = 5 min after buprenorphine total doses of 160 μg i.t.; 3 = 5 min after buprenorphine total doses of 450 μg i.t.; 4 = 5 min after fentanyl 150 μg i.t.; 5 = 5 min after naloxone total dose 4 mg i.v.

135 mm Hg from 145 mm Hg and HR to 75 beat min^{-1} from 80 beat min^{-1} (fig. 4).

Buprenorphine i.t. had only a small depressant effect on MAP and HR, and after the larger dose (1050 μg i.t.) mean MAP was depressed to only 150 mm Hg from the control value of 175 mm Hg, while HR decreased from 150 to 125 beat min^{-1}. After i.t. buprenorphine, fentanyl 150 μg i.t. caused no further significant depression of either MAP or HR.

Naloxone

After naloxone 2 mg i.v., in the preparations receiving buprenorphine i.v. and fentanyl i.v. tibial Aδ and C reflexes returned to 51.3 % and 56.9 % of control values and radial Aδ and C reflexes returned to 49.5 % and 53.0 % respectively; in the preparations receiving opioids i.t., tibial Aδ and C reflexes returned to 76.6 % and 88.9 % of control values, respectively. These reflexes all returned to control values after the second dose of naloxone (total dose 4 mg). Naloxone 4 mg i.v. was required also to reverse fully the depressant effects of buprenorphine on MAP and HR.

DISCUSSION

This study clearly shows that, in common with opioid μ agonists, buprenorphine administered i.t. abolished the C fibre-mediated somatosympathetic reflexes. Unlike the μ agonists, it does not completely eliminate the Aδ reflexes,—that is, there is a plateau or ceiling effect for small myelinated fibre-mediated responses. However, when administered i.v., buprenorphine shows a smaller selectivity in depressing C reflexes compared with the i.t. route, and it has a ceiling effect for both Aδ and C fibre-mediated responses. Hence both the selectively and total effects of buprenorphine are in marked contrast with the pure μ agonists, with which selectivity for C reflexes and abolition of both Aδ and C responses occur after administration by i.v. and i.t. routes [8, 9].

A further increase in the dose of buprenorphine i.v. may possibly produce more depression of the Aδ and C reflexes. However, the dose used in the present study was 100 μg kg^{-1} i.v., which is a very large dose. Moreover, after a dose of 20 μg kg^{-1} i.v. there was only a small further reduction in both Aδ and C reflexes with greater doses. Thus, in therapeutic terms, a ceiling effect probably exists, as the dose–response curves for i.v. buprenorphine suggest that a greater depression leading to abolition of the Aδ and C fibre-mediated somatosympathetic reflexes is unlikely to occur. Moreover, Kato, Saeki and Ogawa [10] reported that, while buprenorphine 6 μg kg^{-1} i.v. had no effect on either A or C fibre-

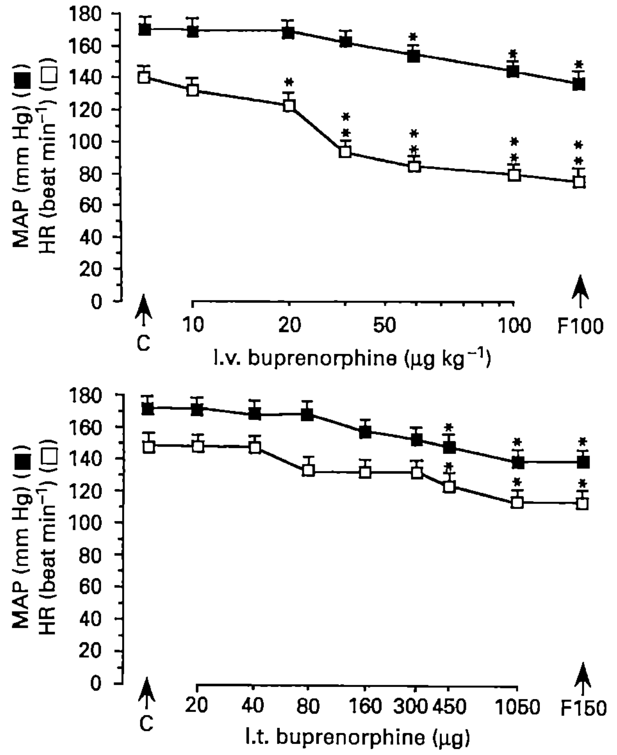

FIG. 4. Cardiovascular changes (mean, SD; $n = 4$) during administration of buprenorphine (i.v. and i.t.) followed by fentanyl 100 μg kg^{-1} i.v. (F100) or 150 μg i.t. (F150). Cumulative dose of buprenorphine is shown on a logarithmic scale. $*P < 0.05$; $**P < 0.01$ compared with control values.

mediated somatosympathetic responses in cats, the somewhat larger dose of 60 μg kg^{-1} markedly depressed the C responses, and that this effect was antagonized by much greater doses up to 300 μg kg^{-1}. Dickenson, Sullivan and McQuay [11] also showed that, in rats, buprenorphine i.v. had no effect on the C fibre-mediated spinal reflexes, even at a dose of 4000 μg kg^{-1} i.v., but for i.t. buprenorphine a dose of only 125 μg depressed the C responses to 46 % of control. Previously, other studies also found in rats that systemic buprenorphine had a bell-shaped dose–response curve for tail-flick [12, 13] and hot-plate tests [14]. In contrast, i.t. buprenorphine was effective against tail-flick and there was no indication of a ceiling effect against the writhing test, but it showed only a weak effect against the hot-plate test [5]. These previously reported differences between the i.v. and i.t. routes are supported by the findings of the present study. The existence of a ceiling effect for the Aδ reflexes for both i.t. and i.v. routes of administration could explain the lower efficacy of this drug in severe pain.

The fact that a ceiling effect may not always be present for a particular action of buprenorphine, as demonstrated in the present study for C fibre-mediated reflexes after i.t. administration, would imply that the drug could have a different mechanism of action for different modalities of effect—for example, in relation to the severe respiratory depression or apnoea reported previously [2–4].

Consistent with previous reports that buprenorphine antagonizes the effect of opioid μ agonists [1], our results also demonstrated that fentanyl had almost no further antinociceptive effect when administered after buprenorphine, either i.t. or i.v. The doses of fentanyl used in this study when administered alone, either i.v. or i.t., have been shown to abolish completely both Aδ and C reflexes [8, 9].

All opioid μ agonists may cause bradycardia and hypotension [15]. Buprenorphine administered i.v. caused a significant depression of arterial pressure and heart rate, but the reduction in heart rate was greater than that in arterial pressure. Cardiovascular depression occurred also after larger doses of i.t. buprenorphine, probably as a result of systemic absorption.

The effects of buprenorphine have been shown to be resistant to naloxone [2, 3, 11, 12]. However, Schmauss and Yaksh [5] found that the effect of i.t. buprenorphine can be antagonized by naloxone. In this study, naloxone was found also to antagonize the effects of buprenorphine, when administered either i.v. or i.t., but a relatively larger dose (4 mg i.v.) was required than the dose of 2 mg i.v. which has been shown to reverse μ agonists in a dog model [8, 9]. This could be attributable to the κ agonist properties of buprenorphine, as has been suggested previously [16].

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LEMAKALIM, A POTASSIUM CHANNEL AGONIST, REVERSES ELECTROPHYSIOLOGICAL IMPAIRMENTS INDUCED BY A LARGE DOSE OF BUPIVACAINE IN ANAESTHETIZED DOGS

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SUMMARY

*We have examined the ability of lemakalim to correct bupivacaine-induced cardiac electrophysiological impairment in an experimental electrophysiological model in closed-chest dogs. Two groups (*n = 6*) of pentobarbitone-anaesthetized dogs were given atropine 0.2 mg kg⁻¹ i.v., and bupivacaine 4 mg kg⁻¹ i.v. over 10 s. Group 2 received also lemakalim 0.03 mg kg⁻¹ i.v. Bupivacaine induced bradycardia, prolonged PR and His–ventricle (HV) intervals, QRS duration, QTc and JTc intervals, decreased left ventricular (LV) dP/dt max and increased LV end-diastolic pressure. Lemakalim reversed bupivacaine-induced PR, HV, QRS, QTc and JTc prolongation, and did not worsen bupivacaine-induced bradycardia and haemodynamic depression. We conclude that lemakalim can antagonize the main deleterious electrophysiological effects induced by a large dose of bupivacaine in anaesthetized dogs.* (Br. J. Anaesth. 1993; **71**: 534–539)

KEY WORDS

Anaesthetics, local: bupivacaine. Pharmacology: potassium channel agonist, lemakalim. Heart: electrophysiology. Toxicity: bupivacaine.

It is now well established that bupivacaine-induced cardiotoxicity (cardiac arrest, cardiovascular collapse, bradycardia, atrioventricular and intraventricular blocks, ventricular arrhythmias) is caused mainly by a marked inhibition of cardiac sodium channels [1] and depression of myocardial contractility [2]. The inhibition of cardiac sodium channels is responsible for a decrease in the maximal upstroke velocity ($\dot{V}$max) of fast action potentials [1] with a dramatic decrease in atrial and ventricular conduction velocities [3, 4]. *In vivo*, the decrease in conduction velocity is responsible for bradycardia, PR lengthening with atrio–His (AH) interval and even more His–ventricle (HV) interval alterations, and QRS widening [5–7]. Moreover, bupivacaine prolongs ventricular effective refractory period [4] and therefore prolongs QT interval *in vivo* [6, 7]. Finally, all these alterations facilitate arcs of functional conduction blocks which explain the occurrence of re-entrant arrhythmias reported previously [4, 8, 9].

Bupivacaine-induced cardiotoxicity is difficult to treat [8, 10]. Thus many experimental studies have been designed to find the best drug to resuscitate cardiotoxic accidents after control of both hypoxia and convulsions [11–15]. We have previously described in anaesthetized dogs that clonidine reversed the impairment of ventricular conduction induced by bupivacaine [16]. However, the mechanism of action of clonidine is unknown.

Lemakalim, the active enantiomer of cromakalim, is an ATP potassium channel opener [17]. It induces arteriolar vasodilatation [18–22], shortens duration of the action potential and restores $\dot{V}$max in cardiac cells previously depolarized, by inducing a more negative maximum diastolic potential [23]. Bupivacaine has opposite *in vitro* electrophysiological effects. Indeed, bupivacaine induces less negative maximum diastolic potential [24] and decreases the $\dot{V}$max of fast action potentials by specifically blocking the cardiac sodium channels in their inactivated states [1]. In other words, the more prolonged the action potential duration, the greater the inhibition of cardiac sodium channels caused by bupivacaine. We may hypothesize that lemakalim could restore the $\dot{V}$max of action potential after exposure to bupivacaine by inducing a more negative maximum diastolic potential, a shorter action potential duration, or both. In this way, lemakalim could therefore normalize the *in vivo* ECG alterations induced by a large dose of bupivacaine. Moreover, in our laboratory we observed, *in vivo* in anaesthetized dogs, that lemakalim shortens indices of ventricular conduction and repolarization and the ventricular effective refractory period [unpublished observations].

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As large doses of bupivacaine prolong PR, AH, HV and QT intervals, and widen QRS complexes, and as lemakalim has opposite effects, we have studied the effects of lemakalim in anaesthetized dogs given a large dose of bupivacaine.

MATERIAL AND METHODS

Animal preparation

The principles for the care and treatment of experimental animals complied with the national guidelines of the French Ministry of Agriculture. We used an experimental electrophysiological model of closed-chest dogs anaesthetized with sodium pentobarbitone [25, 26]. Twelve mongrel dogs of both sexes, weights 10–15 kg, were anaesthetized with sodium pentobarbitone 40 mg kg^{-1} i.v. The trachea was intubated and the lungs ventilated mechanically with room air (74052, B. Braun, Melsungen, Germany). Body temperature was maintained at 38±0.5 °C with an MR 450 rewarming humidifier device (Fisher and Paykel Ltd, Auckland, New Zealand). We have demonstrated previously that each measured variable in this anaesthetized model remains stable over the duration of the study [7, 16].

The animals were instrumented as described previously [27]. ECG recordings were taken from standard lead II. A 6-French gauge bipolar electrode catheter (USCI, C. R. Bard, Inc., Billerica, MA, U.S.A.) was introduced via the femoral vein under fluoroscopy into the right ventricle, close to the interventricular septum near the tricuspid valve to record the His-bundle electrogram [26]. Drugs were administered via a 6-French gauge venous catheter in the contralateral femoral vein. A 5-French gauge Teflon catheter (Plastimed, Saint Leu la Forêt, France) was inserted into the femoral artery and advanced into the descending aorta to sample arterial blood for measurement of blood-gas tensions (pH > 7.35, $Pa_{O_2} > 11.5$ kPa, $Pa_{CO_2} < 5.3$ kPa) (Instrument Laboratory 1306 *p*H/blood gas analyzer, Italy), and for the assay of plasma concentrations of bupivacaine. The contralateral femoral artery was cannulated with a 6-French gauge double high fidelity micromanometer (Millar Instruments, Houston, TX, U.S.A.) advanced into the left ventricle under fluoroscopy to measure left ventricular and aortic pressures. The procedure of animal preparation required about 30 min.

Measurements

The following electrophysiological measurements (expressed in ms) were made: cardiac cycle duration (R–R interval); PR interval measured from the onset of the P wave to the Q wave of the QRS complex; AH interval measured from the onset of atrial depolarization to the His-bundle electrogram of the endocavitary lead; HV interval measured from the His-bundle electrogram of the endocavitary lead to the Q wave of ECG lead II; QRS duration. The indices of ventricular repolarization were QT interval corrected by R–R interval (QTcorr. = QT/$\sqrt{}$R–R, Bazett formula) and JT interval measured from the end of QRS to the end of T wave corrected by R–R interval (JTcorr. = JT/$\sqrt{}$R–R). The following haemodynamic variables were measured: mean aortic pressure (MAoP, mm Hg); left ventricular end-diastolic pressure (LVEDP, mm Hg); peak of the first derivative of left ventricular pressure (LVd*P*/d*t*max, mm Hg s^{-1}) as an index of contractility [28] derived with a Gould differentiator. All these variables were recorded on an ES 1000 polygraph (100 mm s^{-1}) (Gould Inc., Oxnard, CA, U.S.A.). The plasma concentration of bupivacaine was measured by high pressure liquid chromatography [29–31].

Experimental procedure

We studied two groups of six dogs. In each animal, a 30-min period was allowed for stabilization of the preparation. Each animal was then given atropine 0.2 mg kg^{-1} i.v. to prevent vagal reactivity; this dose has been demonstrated to inhibit completely any cardiac response to stimulation of the cervical vagus nerves in our preparation and in another study [32]. As described previously, atropine does not modify the electrophysiological and mechanical changes induced by bupivacaine [33].

All dogs also received saline solution 3.5 ml kg^{-1} h^{-1} i.v. and bupivacaine 4 mg kg^{-1} i.v. (Bupivacaine HCl 0.5 %, Laboratoires R. Bellon, Neuilly-sur-Seine, France) over 10 s, 5 min after the atropine injection. We have reported previously that this dose of bupivacaine induces marked myocardial depression and major electrophysiological changes without causing cardiovascular collapse or immediate cardiac death [6]. Dogs in group 1 received bupivacaine only; those in group 2 received, 1 min after the bupivacaine, lemakalim 0.03 mg kg^{-1} i.v. (provided by SmithKline Beecham Laboratoires Pharmaceutiques, Unité de Recherche, St-Grégoire, France) over 1 min period.

Electrophysiological and haemodynamic variables were recorded before and 5 min after administration of atropine (just before bupivacaine administration (0 min: baseline)), and 1, 2, 3, 4, 5, 10, 15 and 30 min after the bupivacaine administration. Arterial blood samples were obtained before and at the end of the bupivacaine injection, and 3, 15 and 30 min later.

Statistical analysis

Results are expressed as mean (SD). The effects of atropine in the two groups, the effects of bupivacaine throughout the study in group 1 and at time 1 min in group 2 were tested using one-way ANOVA for repeated measures, followed by contrast study and completed with Bonferroni's correction [34]. Data from group 2 were compared with those of group 1 to compare the effects of bupivacaine between the two groups at time 1 min, and then to test the effects of lemakalim using two-way ANOVA for repeated measures, followed by contrast study and completed with Bonferroni's correction [34]. $P < 0.05$ was considered statistically significant. All the results were analysed on a micro Vax II computer (Digital Equipment Corporation, Maynard, MA, U.S.A.) with a 1990 version 6 SAS computer program (SAS Institute Inc., Cary, NC, U.S.A.).

TABLE I. *Electrophysiological variables (mean (SD)). Group 1 = bupivacaine; group 2 = bupivacaine+lemakalim.* $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, *compared with group* 1

	Before atropine	Baseline	1 min	2 min	3 min	4 min	5 min	10 min	15 min	30 min
R–R (ms)										
Group 1	412.3	407.5	459.2	479.2	479.2	484.2	487.5	477.5	472.5	475.0
	(97.4)	(99.1)	(118.8)	(125.5)	(130.5)	(131.1)	(136.8)	(134.5)	(134.1)	(143.7)
Group 2	325.8	325.8	375.8	377.5	370.8	353.3	340.0	325.8	328.3	319.2
	(64.7)	(64.5)	(79.8)	(82.0)	(81.0)	(74.7)	(67.2)	(61.7)	(63.7)	(68.7)
PR (ms)										
Group 1	97.5	93.3	137.2	140.8	138.3	138.3	136.7	125.3	118.3	112.5
	(3.5)	(7.5)	(10.6)	(14.6)	(14.0)	(14.0)	(14.7)	(16.4)	(16.6)	(13.7)
Group 2	85.3	85.3	134.2	117.0***	108.5***	96.7***	90.8***	85.0***	84.5**	83.7*
	(5.2)	(5.2)	(8.6)	(10.3)	(7.1)	(4.1)	(3.8)	(4.5)	(5.4)	(6.5)
AH (ms)										
Group 1	62.0	58.2	69.0	71.2	71.2	71.2	71.6	71.2	70.2	67.5
	(3.4)	(4.7)	(6.8)	(8.0)	(8.0)	(8.0)	(8.2)	(7.6)	(5.7)	(5.0)
Group 2	54.2	54.2	60.8	61.7	63.7	63.8	63.3	59.7	59.5	59.2
	(5.8)	(5.8)	(4.9)	(5.2)	(6.4)	(3.8)	(4.5)	(4.1)	(4.6)	(4.9)
QTcorr.										
Group 1	333.5	331.0	423.5	434.7	438.8	435.2	430.3	405.8	386.3	376.5
	(16.3)	(14.2)	(45.0)	(49.6)	(46.9)	(44.0)	(44.3)	(34.0)	(35.6)	(29.8)
Group 2	330.2	331.3	467.0	401.0**	352.7***	328.3***	314.5***	306.2***	300.3**	306.5*
	(8.9)	(9.4)	(49.5)	(70.2)	(41.8)	(29.9)	(19.3)	(13.8)	(12.2)	(9.8)
JTcorr.										
Group 1	234.7	235.0	249.3	260.5	264.2	262.8	260.8	264.0	262.7	262.3
	(7.2)	(9.7)	(25.7)	(28.7)	(27.9)	(25.7)	(23.6)	(30.7)	(33.8)	(31.1)
Group 2	225.5	226.8	256.7	242.8*	230.3**	223.2**	220.5**	215.8*	211.3*	212.3
	(10.1)	(9.0)	(16.3)	(24.4)	(13.0)	(11.1)	(10.2)	(10.4)	(11.8)	(11.2)

TABLE II. *Haemodynamic variables (mean (SD)). Group 1 = bupivacaine; group 2 = bupivacaine+lemakalim*

	Before atropine	Baseline	1 min	2 min	3 min	4 min	5 min	10 min	15 min	30 min
MAoP (mm Hg)										
Group 1	145.5	123.0	115.8	109.7	112.5	118.5	117.2	114.8	117.5	119.2
	(16.3)	(30.1)	(22.3)	(24.2)	(22.0)	(30.1)	(30.0)	(26.7)	(27.2)	(26.0)
Group 2	140.2	138.5	84.0	77.7	64.3	68.3	78.2	85.3	93.2	109.5
	(10.9)	(11.0)	(23.9)	(21.9)	(18.5)	(11.3)	(11.4)	(14.4)	(17.3)	(19.1)
LVdP/d$t$max (mm Hg s^{-1})										
Group 1	1625.0	1691.7	829.2	875.0	941.7	966.7	1008.3	1041.7	1108.3	1283.3
	(176.8)	(300.7)	(107.7)	(144.1)	(182.8)	(213.7)	(213.1)	(190.8)	(231.1)	(150.5)
Group 2	1308.3	1441.7	591.7	716.7	775.0	900.0	1016.7	1141.7	1191.7	1358.3
	(201.0)	(352.7)	(329.3)	(441.2)	(446.9)	(428.9)	(375.0)	(382.6)	(390.4)	(387.8)
LVEDP (mm Hg)										
Group 1	5.5	8.2	14.8	14.8	13.8	13.3	12.0	12.0	10.2	9.5
	(0.7)	(2.9)	(4.3)	(3.8)	(3.5)	(2.4)	(3.4)	(4.5)	(3.1)	(4.1)
Group 2	3.8	3.3	10.7	8.5	6.3	4.5	3.2	3.2	2.5	2.7
	(3.4)	(3.1)	(1.0)	(6.0)	(5.3)	(3.0)	(2.2)	(2.5)	(2.2)	(2.7)

RESULTS

Atropine did not significantly modify the electrophysiological and haemodynamic variables in the two groups (tables I, II). In group 1, bupivacaine induced non-significant bradycardia, a greater than 50% increase in PR interval ($P < 0.001$ at 1 min; $P < 0.01$ from 2 to 5 min; $P < 0.05$ at 10 min) and a non-significant increase in AH interval. Bupivacaine prolonged the HV interval by more than 100% ($P < 0.001$ from 1 to 5 min; $P < 0.01$ at 10 and 15 min) (fig. 1), caused a widening (> 100%) of the QRS complex ($P < 0.01$ at 1 and 2 min; $P < 0.05$ from 3 to 10 min), and prolonged the QTcorr. interval ($P < 0.05$ from 1 to 15 min) (table I). Similarly, bupivacaine impaired the haemodynamic state: it decreased LVdP/d$t$max ($P < 0.05$ from 1 to 10 min) and increased LVEDP ($P < 0.05$ from 1 to 4 min) by more than 50%. Bupivacaine decreased MAoP (ns). Similar effects of bupivacaine were observed in group 2 at 1 min before administration of lemakalim.

Lemakalim did not modify R–R and AH intervals (table I). In contrast, the increase in PR interval induced by bupivacaine was significantly improved by lemakalim. Lemakalim significantly and quickly reversed the increase in HV interval and the QRS widening induced by bupivacaine (fig. 1) and corrected the alterations in QTcorr. and JTcorr. induced by bupivacaine (table I). Although MAoP decreased more in group 2, lemakalim did not significantly modify the haemodynamic alterations induced by bupivacaine (table II).

All bupivacaine plasma concentrations were in the toxic range from the end of bupivacaine administration to 15 min. There was no significant difference between the two groups (table III).

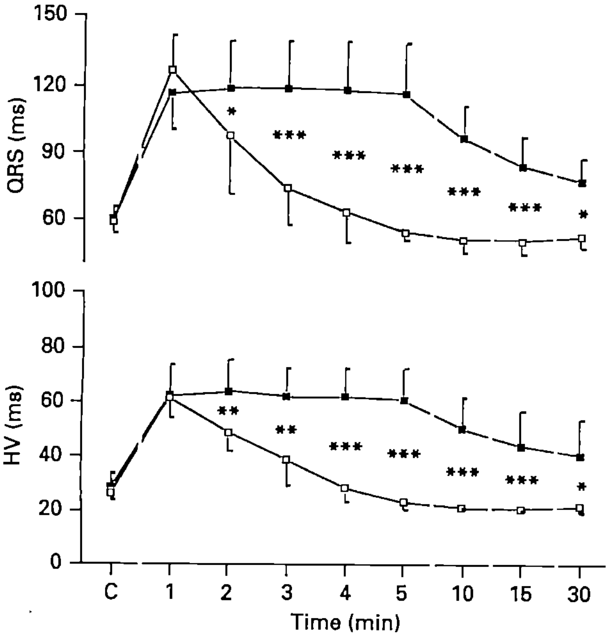

FIG. 1. Comparison of the effects of bupivacaine given alone to dogs in group 1 (■) and given with lemakalim to dogs in group 2 (□) on QRS duration (QRS) and HV interval (HV) (means, SD). C = Control (before bupivacaine administration). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; between groups.

TABLE III. *Plasma concentrations of bupivacaine (mean (SD)). Group 1 = bupivacaine; group 2 = bupivacaine + lemakalim. 0 min = immediately after bupivacaine injection*

	Bupivacaine conc (μg ml^{-1})			
	0 min	3 min	15 min	30 min
Group 1	58.2 (7.7)	5.4 (1.7)	2.2 (1.3)	1.4 (0.9)
Group 2	53.8 (10.1)	8.5 (3.8)	2.1 (0.8)	1.6 (0.6)

DISCUSSION

We have shown that lemakalim corrected the electrophysiological disturbances induced by bupivacaine on atrio–ventricular conduction, conduction and repolarization of ventricles. The dose of bupivacaine 4 mg kg^{-1} we used induced alterations similar to those reported elsewhere [5–7, 9, 12–16]. Moreover, plasma concentrations of bupivacaine were in the toxic range—that is, they exceeded 2 μg ml^{-1}—from the end of bupivacaine injection to 15 min [10]. Therefore, we can assume that our model is suitable for studying *in vivo* bupivacaine cardiotoxicity.

HV interval and QRS duration were impaired dramatically by bupivacaine. HV interval and QRS duration are known to be correlated with the His–Purkinje system and ventricular conduction velocities, respectively [26, 35]. As lemakalim normalized HV interval and QRS duration after bupivacaine administration, our results suggest that lemakalim restored these conduction velocities. Moreover, the main mechanism of ventricular arrhythmias induced by local anaesthetics and by class 1b and 1c antiarrhythmic drugs is slowing of ventricular conduction velocity, inducing arcs of functional conduction blocks with re-entry phenomena around them [4, 36, 37]. Indeed, using ventricular mapping in anaesthetized dogs, Anderson and co-workers [37] demonstrated that ventricular tachycardias are induced with large plasma concentrations of lignocaine. These authors also reported that activation patterns obtained just before the onset of ventricular tachycardias simultaneously showed marked slowing of ventricular conduction velocity and QRS widening [37]. Using left ventricular epicardial mapping in rabbit hearts, we have demonstrated previously that bupivacaine markedly slows ventricular conduction velocity and induces re-entrant arrhythmias around the functional arcs of conduction blocks [4]. Therefore, as lemakalim improved bupivacaine-induced QRS widening and HV prolongation, we postulate that lemakalim may prevent the occurrence of re-entrant ventricular arrhythmia induced by a toxic dose of bupivacaine.

Lemakalim also reversed alterations in ventricular repolarization induced by bupivacaine. Indeed, the prolongation of QTcorr. and JTcorr. intervals was corrected quickly by administration of lemakalim. Kasten [38] studied anaesthetized dogs and suggested that ventricular arrhythmias induced by bupivacaine are similar to torsades de pointes. This author reported that the occurrence of torsades de pointe was facilitated by QT prolongation and refractoriness dispersion induced by bupivacaine [38]. Thus we may postulate also that lemakalim might protect against the occurrence of this type of arrhythmia after bupivacaine-induced cardiotoxicity. Moreover, some *in vitro* and *in vivo* studies have demonstrated that potassium channel openers are efficient antiarrhythmic drugs when repolarization is delayed [39–42].

Different mechanisms might be involved in the beneficial effects of lemakalim in the reversal of bupivacaine-induced cardiotoxicity. Correction of the prolongation of ventricular repolarization seems to be clear, because potassium channel openers or the activation of ATP potassium current decreases the duration of action potentials [23, 43–46]. In contrast, the improvement in ventricular conduction induced by lemakalim after administration of bupivacaine remains unclear. One could suggest that lemakalim increases the $\dot{V}$max of fast action potentials by inducing hyperpolarization [47]. However, no study has reported that potassium channel agonists induce hyperpolarization associated with an increase in $\dot{V}$max, except in cardiac cells partially depolarized by ischaemia [23, 48]. Our dogs were believed not to have myocardial ischaemia. However, it has been reported that bupivacaine depolarizes the cardiac membrane potential [24], therefore we may postulate that lemakalim restores a more negative maximum diastolic potential and corrects the dramatic decrease in $\dot{V}$max induced by bupivacaine. Another mechanism could be involved. Clarkson and Hondeghem [1] demonstrated that bupivacaine preferentially blocks cardiac sodium channels during diastole in their inactivated states. As lemakalim decreases the duration of action potentials, it could be postulated that lemakalim decreases block of cardiac sodium channels in their inactivated states and therefore lemakalim could restore $\dot{V}$max. However, our *in vivo* model did not permit confirmation of these hypotheses. Further studies are therefore required to elucidate the mechanisms responsible for lemakalim-induced shortening of HV and QRS in anaesthetized dogs given a large dose of bupivacaine.

The increase in PR interval induced by bupivacaine was corrected by lemakalim because the HV interval was decreased, while the AH interval was not modified. In addition, there was no worsening of heart rate or other haemodynamic variables. Thus it appears that lemakalim is more efficient than clonidine in reversing bupivacaine cardiotoxicity. Indeed, clonidine also improves ventricular conduction in anaesthetized dogs, but enhances bradycardia, does not modify the PR interval because it prolongs the AH interval, and tends to worsen the haemodynamic depression induced by bupivacaine [16]. Nevertheless, care must be taken before extrapolating these results to the clinical setting. It must be emphasized that the dogs were anaesthetized and received atropine. In addition, the beneficial effects of lemakalim were observed in dogs that had suffered neither cardiovascular collapse nor ventricular arrhythmias. In contrast, the clinical resuscitation of cardiotoxic accidents necessitates oxygenation, treatment of convulsions and specific cardiac resuscitation [10], which requires simultaneous correction of electrophysiological and haemodynamic disturbances [16]. Indeed, despite the production of little cardiovascular change in our study, it must be emphasized that lemakalim or other ATP potassium channel openers induce arteriolar vasodilatation. In the absence of catecholamines, their use may therefore precipitate cardiovascular collapse after bupivacaine overdosage. Furthermore, except in the case of delayed repolarization induced by drugs such as bupivacaine, the use of lemakalim or of other ATP potassium channel openers may facilitate arrhythmias [49, 50].

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FENTANYL INHIBITS THE UPTAKE OF [^{3}H]NORADRENALINE IN CULTURED NEURONAL CELLS

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SUMMARY

We have examined how fentanyl modulates [^{3}H]noradrenaline uptake in two cultured neuronal cell preparations, the human neuroblastoma SH-SY5Y and the rat phaeochromocytoma PC12. Fentanyl produced a significant, dose-dependent inhibition of [^{3}H]noradrenaline uptake at concentrations in excess of 0.1 µmol litre^{-1} ($P < 0.05$) and 0.3 µmol litre^{-1} ($P < 0.05$) for PC12 and SH-SY5Y cells, respectively. However, these values exceed the serum concentration of fentanyl required to produce analgesia. At the maximum concentration examined (100 µmol litre^{-1}), fentanyl produced 85–95% inhibition of uptake. This effect was not antagonized by naloxone, implying a non-opioid mechanism of action. Imipramine 1 µmol litre^{-1} reduced [^{3}H]noradrenaline uptake by 65–70% but morphine, in contrast to fentanyl, had no effect ($P > 0.1$). (Br. J. Anaesth. 1993; **71**: 540–543)

KEY WORDS

Analgesics: fentanyl. Sympathetic nervous system: noradrenaline uptake.

The precise cellular mechanisms by which opioids modulate pain transmission in the central nervous system are unknown. Occupation of presynaptic opioid receptors reduces evoked neurotransmitter release, and this has been demonstrated in a variety of tissue preparations and for different neurotransmitters [1]. However, there is only limited evidence that opioids modulate neurotransmitter uptake. For instance, morphine, methadone, codeine and thebaine reduced [^{3}H]noradrenaline uptake in rabbit brain synaptosomes [2]. Similarly, methadone and morphine reduced [^{3}H]5-hydroxytryptamine uptake in rat brain synaptosomes, but only methadone reduced [^{3}H]noradrenaline uptake [3]. In addition, the importance of the modulation of neuronal amine uptake in the production of analgesia remains to be established.

In this study we have used two noradrenergic cell lines—a human neuroblastoma, SH-SY5Y [4, 5] and a rat phaeochromocytoma, PC12 [6]—to examine the effect of fentanyl on [^{3}H]noradrenaline uptake, and to compare this with the effects of morphine and imipramine. Isolated clonal cells are homogeneous and this is a useful attribute in the study of neurotransmitter modulation. Furthermore, they are not associated with problems such as diffusion limitations and unwanted cellular interactions that may occur with brain slice preparations. These cells are relatively easy to culture and are capable of uptake and release of noradrenaline [7, 8]. Moreover, SH-SY5Y cells express μ and δ opioid receptors [9], but the exact receptor profile of PC12 remains unknown.

A preliminary account of this work has been published as an abstract [10].

MATERIALS AND METHODS

Cell culture and source of reagents

SH-SY5Y human neuroblastoma cells (obtained from J. L. Beidler, Sloan-Kettering Institute for Cancer Research, Rye, NY, U.S.A.), passages 71–80, were routinely maintained in minimum essential medium supplemented with L-glutamine 2 mmol litre^{-1}, penicillin 100 iu ml^{-1}, streptomycin 100 µg ml^{-1}, fungizone 2.5 µg ml^{-1} and 10% (v/v) fetal calf serum in 5% carbon dioxide/humidified air at 37 °C. Stock cultures were fed twice weekly and passaged weekly. The cell monolayers were harvested by treatment with 0.05% trypsin–0.02% EDTA, cultured in six-well plates at a seeding density of 2.5×10^5 cells well^{-1} and grown until confluent (5–7 days).

PC12 rat phaeochromocytoma cells (passages 13–16) were routinely maintained in Dulbecco's minimum essential medium supplemented with penicillin 100 iu ml^{-1}, streptomycin 100 µg ml^{-1}, fungizone 2.5 µg ml^{-1}, 10% (v/v) horse serum and 5% (v/v) fetal calf serum. PC12 cells were otherwise treated in the same way as SH-SY5Y cells.

Minimum essential medium, fetal calf serum, glutamine, penicillin plus streptomycin, fungizone, trypsin–EDTA, and six-well tissue-culture plates (Nunc) were from Life Technologies (Uxbridge, U.K.). L-[7,8-^{3}H]noradrenaline 37 Ci mmol^{-1} was from Amersham Life Sciences (U.K.). Fentanyl citrate, morphine sulphate, naloxone hydrochloride and imipramine hydrochloride were from Sigma Chemical Company Ltd (Dorset, U.K.).

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Measurement of [^{3}H]noradrenaline uptake

All experiments were performed at 37 °C in Krebs–HEPES buffer of the following composition (mmol litre^{-1}): Na$^+$ 143.4, K$^+$ 4.7, Ca^{2+} 2.5, Mg^{2+} 1.2, Cl$^-$ 125.6, HCO$_3^-$ 25.0, H$_2$PO$_4^{2-}$ 1.2, SO$_4^{2-}$ 1.2, glucose 11.7, HEPES 10.0, ascorbic acid 0.2, monoamine oxidase inhibitor (pargyline) 0.2. Confluent cell cultures were washed twice in fresh buffer and then incubated in buffer containing [^{3}H]noradrenaline ([^{3}H]NA) 48 nmol litre^{-1}, 0.5 ml well^{-1} ($\sim 2.1 \times 10^6$ d.p.m.). Each well was incubated for a fixed period: 5, 10, 20, 30, 60 or 90 min for SH-SY5Y and 15, 30, 45 or 60 min for PC12. After incubation, the cell monolayers were washed twice with buffer (1 ml) to remove extracellular [^{3}H]NA. [^{3}H]NA taken up by the cells was extracted by digesting the cells with perchloric acid 0.4 mol litre^{-1} (1.25 ml), and the amount taken up expressed as a percentage of the amount of [^{3}H]NA in the incubation buffer at the start of the experiment. Radioactivity was measured by liquid scintillation spectrophotometry (Packard 1900 TR) with optiphase X (LKB Scintillation Products) as a scintillant.

Modulation of [^{3}H]noradrenaline uptake

The effect of fentanyl on [^{3}H]NA uptake in both cell lines was examined by incubating the cell monolayers with [^{3}H]NA 48 nmol litre^{-1} and fentanyl 10^{-7}–10^{-4} mol litre^{-1} for 1 h. Morphine 1 µmol litre^{-1}, naloxone 1 µmol litre^{-1} and imipramine 1 µmol litre^{-1} were also added in various combinations.

All experiments except those to determine the maximum uptake of [^{3}H]NA and the dose–response effect of fentanyl were performed in duplicate.

Statistical analysis

Data are expressed as mean (SEM) and were analysed using ANOVA and Student's paired or unpaired *t* test as appropriate and considered significant when $P < 0.05$. Curve fitting for the estimation of half-maximum uptake and IC$_{50}$ values was performed by non-linear regression using "Graphpad".

RESULTS

Both cell lines were capable of the uptake of [^{3}H]NA, with a maximum uptake of approximately 26 % and 7.5 % for SH-SY5Y cells and PC12 cells, respectively (fig. 1). Half-maximum uptake occurred at 5.7 (0.2) min ($n = 5$) and 9.3 (1.5) min ($n = 5$) for SH-SY5Y cells and PC12 cells, respectively (unpaired *t* test, $P > 0.05$). Maximum uptake occurred within 60 min and therefore all remaining experiments were performed after a 60-min incubation period.

Significant inhibition of [^{3}H]NA uptake by fentanyl occurred from 0.1 µmol litre^{-1} in PC12 cells (paired *t* test, $P < 0.05$) and 0.3 µmol litre^{-1} in SH-SY5Y cells (paired *t* test, $P < 0.05$) (fig. 2). The inhibition by fentanyl was dose-dependent (ANOVA, $P < 0.05$) and at the maximum concentration used (100 µmol litre^{-1}), 85–95 % inhibition was observed. Assuming a maximum inhibitory effect of 100 %, the IC$_{50}$ values for fentanyl were 5.37 µmol litre^{-1} and 2.09 µmol litre^{-1} in SH-SY5Y and PC12 cells, respectively.

In order to assess the specificity and mechanism of fentanyl inhibition, we examined the effects of morphine, naloxone and the uptake-1 inhibitor, imipramine (fig. 3). Imipramine 1 µmol litre^{-1} produced a significant depression of uptake (65–70 %) in both cell lines, compared with 26–38 % inhibition by the same concentration of fentanyl. Morphine 1 µmol litre^{-1} and naloxone 1 µmol litre^{-1} alone had no significant effect. More importantly, naloxone did not antagonize fentanyl-mediated inhibition of noradrenaline uptake.

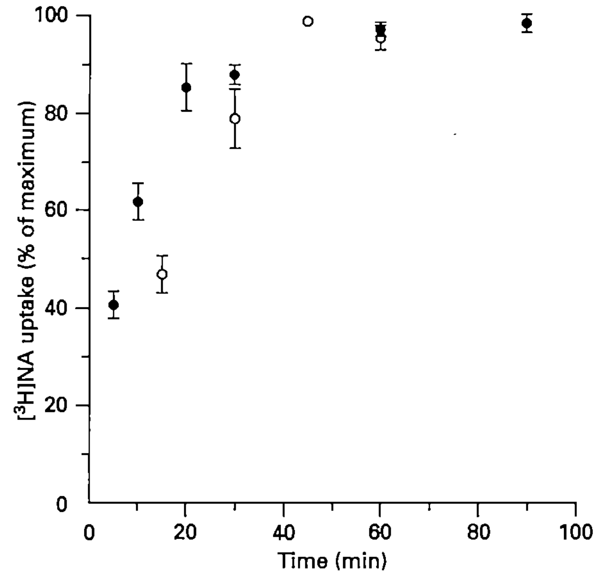

FIG. 1. Time course of [^{3}H]noradrenaline ([^{3}H]NA) uptake in SH-SY5Y (●) and PC12 (○) cells (mean, SEM) ($n = 5$). Cells exposed to [^{3}H]NA 48 µmol litre^{-1} showed typical maximum and half-maximum uptake at approximately 60 min and 4–6 min, respectively. Maximum uptake in SH-SY5Y and PC12 cells was approximately 26 % and 7.5 %, respectively.

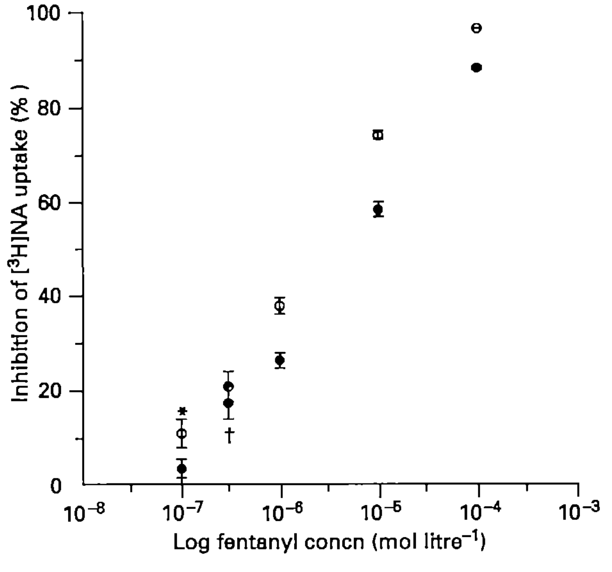

FIG. 2. Inhibition of [^{3}H]noradrenaline ([^{3}H]NA) uptake by fentanyl (mean, SEM) ($n = 5$–12). * $P < 0.05$ between PC12 (○) and control group (no fentanyl); † $P < 0.05$ between SH-SY5Y (●) and control group (no fentanyl). Maximum serum concentrations of fentanyl which occur in clinical anaesthesia are less than 0.6 µmol litre^{-1}.

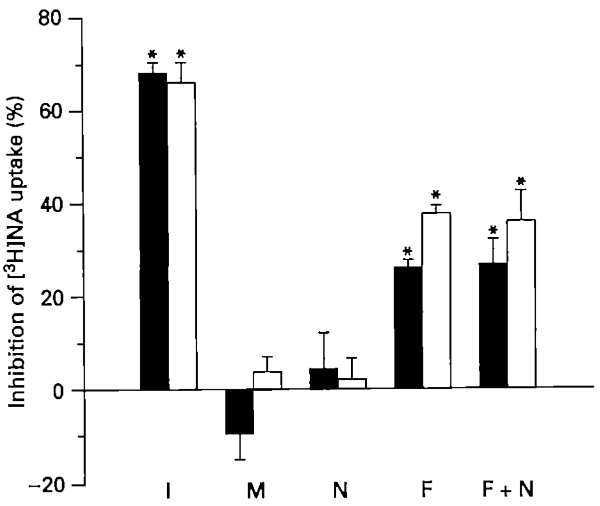

FIG. 3. Effect of fentanyl (F), morphine (M), naloxone (N) and imipramine (I) (all 1 μmol litre^{-1}) on [^{3}H]noradrenaline ([^{3}H]NA) uptake in SH-SY5Y (■) and PC12 (□) cells (mean, SEM) (n = 5–10). *$P < 0.05$ between drug group and control (no drug). Morphine and naloxone had no effect. Naloxone did not antagonize fentanyl inhibition of uptake.

DISCUSSION

Undifferentiated SH-SY5Y and PC12 cells are both capable of the uptake of [^{3}H]noradrenaline, with a maximum uptake of approximately 26.0% and 7.5%, respectively. In addition, we have shown a clear, dose-dependent inhibition of noradrenaline uptake by fentanyl in both noradrenergic neuronal cell lines. However, this inhibition was not antagonized by naloxone and is therefore not mediated via the opioid receptor. As would be expected, imipramine 1 μmol litre^{-1} produced 65–70% inhibition of uptake, indicating the presence of the uptake-1 system in these cells.

The ability of SH-SY5Y cells to take up [^{3}H]NA is in agreement with the findings of Scott and colleagues, who have shown a maximum uptake of 18% in differentiated SH-SY5Y cells [11], but no studies were made on the modulation of uptake. A maximum uptake of approximately 7.5% in PC12 cells contrasts with the findings of Green and Rein, who achieved a maximum uptake of 17–36% [7], although maximum uptake depends on seeding density. They also examined the K_m and Vmax of [^{3}H]NA uptake in PC12 cells and demonstrated that cell differentiation does not alter the kinetics of the uptake system itself [6].

The inactivity of morphine on [^{3}H]NA uptake in this study is in agreement with the work of Slotkin, Seidler and Whitmore, who were unable to show an effect of morphine 10^{-4} mol litre^{-1} on [^{3}H]NA uptake in rat brain synaptosomes [3], although it did have a small (20%) inhibitory effect on [^{3}H]5-hydroxytryptamine uptake. However, several studies using synaptosomes have shown an inhibitory effect of morphine on [^{3}H]NA uptake, but only in large concentrations (10^{-4} mol litre^{-1}) [2, 12]. Furthermore, Montel and Starke demonstrated that several opioids, including morphine 10^{-6} mol litre^{-1}, inhibited neuronal uptake of [^{3}H]NA in a perfused, isolated rabbit heart [13]. The effect of morphine was not antagonized by naloxone, also indicating a mechanism of action independent of the opioid receptor.

Catecholamine uptake by neurones occurs in two, distinct processes [14]. The first system transports the amine from the synaptic cleft across the cell membrane and into the cytoplasm, requires a sodium–potassium-activated ATPase and is blocked by imipramine. This system contributes to the inactivation of the synaptic neurotransmitter effect. The second system transports the cytoplasmic amine into the storage vesicle, requires a magnesium-activated ATPase and is inhibited by reserpine. The second system is responsible for the maintenance of transmitter stores. The mechanism of fentanyl inhibition of [^{3}H]NA uptake is unknown, but may involve direct interaction of the opioid with the cell membrane uptake system, similar to that of imipramine. Considerable structural variability exists amongst the tricyclic and atypical antidepressant drugs, all of which block amine uptake [15]. The problem is further complicated by the possibility that two membrane [^{3}H]NA uptake systems may exist [16]. Although there is no evidence that fentanyl (unlike reserpine) depletes noradrenaline stores, interference by fentanyl in vesicular uptake, although unlikely, cannot be excluded and further work is required to determine the exact site of fentanyl inhibition.

One question that remains is whether or not inhibition of noradrenaline uptake is of any clinical importance in the production of analgesia. Whilst we have shown that fentanyl produces a significant effect on [^{3}H]NA uptake in serum concentrations which occur in clinical anaesthesia, such concentrations are very great and restricted to those patients who have received a large bolus of fentanyl (50–100 μg kg^{-1}, producing serum concentrations of 0.1–0.6 μmol litre^{-1} 1 min after injection) [17]. Furthermore, doses of approximately 30 μg kg^{-1} have produced CSF concentrations of only 7.5 nmol litre^{-1} [18]—a concentration 10-fold smaller than that at which we have demonstrated an effect. The serum concentration of fentanyl that produces analgesia is 1–3 ng ml^{-1} (approximately 3–10 nmol litre^{-1}) [19]. Large concentrations of opioid agonists and antagonists have been shown to inhibit amine uptake in synaptosomes [2, 3, 12, 20], but there appears to be no correlation between the ability of these drugs to block amine uptake and their analgesic efficacy. Indeed, in one study naloxone and morphine inhibited noradrenaline uptake in rabbit brain synaptosomes in similar concentrations, suggesting that the inhibition of noradrenaline uptake by opioids does not contribute significantly to the production of analgesia [2]. This contrasts with *in vivo* and *in vitro* evidence using tramadol hydrochloride, a synthetic opioid with an analgesic potency comparable to that of codeine [21]. This drug binds with some selectivity for μ receptors (K_1 = 2.10 μmol litre^{-1}) and inhibits uptake of noradrenaline (K_1 = 0.79 μmol litre^{-1}) and 5-hydroxytryptamine (K_1 = 0.99 μmol litre^{-1}) [22, 23]. Unlike the commonly used opioids, tramadol in clinical use is not associated with significant side effects such as respiratory depression and it appears that it produces analgesia by both an opioid (μ receptor) and a non-opioid (inhibition of amine uptake) mechanism.

In conclusion, we have demonstrated a clear inhibition of noradrenaline uptake by fentanyl, although a significant effect occurred only with serum concentrations of fentanyl greater than those that produce analgesia. However, it may be of some importance in those patients receiving large doses, for instance, during cardiac anaesthesia. Whilst the role of amine uptake inhibition in the production of analgesia is unclear, it may be important for some analgesic drugs.

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MECHANISMS OF THE RELAXANT ACTION OF KETAMINE ON ISOLATED PORCINE TRACHEALIS MUSCLE

L. E. WILSON, D. J. HATCH AND K. REHDER

SUMMARY

Ketamine is a potent bronchodilator, but its mode of action is unclear. We have studied the effect of ketamine on the peripheral vagus nerve motor pathway of isolated porcine trachealis muscle. Postsynaptic nicotinic cholinergic receptors of the intramural ganglia were stimulated selectively with 1,1-dimethyl-4-phenyl-piperazinium iodide, postganglionic nerve fibres with electrical field stimulation (in the presence of hexamethonium) and muscarinic cholinergic receptors with acetylcholine (in the presence of tetrodotoxin). Ketamine 10^{-4} mol litre^{-1} significantly shifted the concentration–response curves of acetylcholine ($P < 0.02$*) and electrical field stimulation (*$P < 0.001$*) to the right and abolished the response to 1,1-dimethyl-4-phenyl-piperazinium iodide (*$P < 0.02$*). Ketamine also caused a concentration-dependent relaxation of muscle strips precontracted with acetylcholine. This was unaffected by propranolol. Ketamine relaxed muscle strips precontracted with potassium chloride, in the absence and presence of atropine. We conclude that ketamine interacts with the peripheral vagus nerve by decreasing the excitability of the postsynaptic nicotinic receptors of the intramural ganglia, and by affecting the muscarinic receptor, smooth muscle, or both. Beta-*$_2$ *adrenoceptors are not involved in the mechanism of relaxation.* (Br. J. Anaesth. 1993; **71**: 544–550)

KEY WORDS

Anaesthetics, intravenous: ketamine. Lung: bronchodilatation.

Ketamine, a phencyclidine derivative, is an anaesthetic agent with known bronchodilator actions [1]. It has been used in the treatment of status asthmaticus and for relief of bronchospasm during general anaesthesia [2–5].

In vitro studies of trachealis and bronchial smooth muscle in various species have shown that ketamine produces concentration-dependent relaxations [6, 7], but the mechanism is unclear. One proposed mode of action is that ketamine may have a direct effect on the contractile properties of the smooth muscle [6]. A beta-adrenergic effect has also been proposed, as in antigen-sensitized dogs the prevention of bronchospasm by ketamine is abolished by propranolol [8]. No beta-adrenoceptor-mediated role in the action of ketamine has been detected *in vitro* [7] and the relaxation of human airway smooth muscle *in vitro* is not dependent on products of the cyclo-oxygenase pathway [7]. Ketamine has been shown to have an inhibitory effect exerted centrally on vagal pathways [9], but no studies have investigated effects on the peripheral vagal motor pathway.

This study was designed to determine the site of action of ketamine on the peripheral vagus nerve motor pathway in isolated porcine trachealis muscle strips. From the central nervous system, preganglionic fibres pass down the vagus nerve to ganglia located in the walls of the airway (fig. 1). On their stimulation, acetylcholine is released and activates nicotinic receptors in the postsynaptic membrane of the ganglia. The stimulus is carried via the postganglionic cholinergic nerves to release acetylcholine which binds to the muscarinic receptors on the smooth muscle (first messenger). As a result of chemical transmission of the signal from the muscarinic receptor to the contractile elements of the smooth muscle (second messengers), the smooth muscle contracts.

Choice of stimuli

Theoretically, ketamine can reduce the contractile response of the muscle by an effect on the central nervous system, the preganglionic fibres, the nicotinic receptors in the postsynaptic membrane of the intramural ganglia, the postganglionic fibres, the muscarinic receptors, the chemical signal transmission between the receptors and the contractile elements, the contractile elements or any combination of the above. In the isolated airway muscle, only the peripheral vagus motor pathway is present and available for examination.

Acetylcholine applied extraneously to the smooth muscle stimulates both the cholinergic nicotinic and the muscarinic receptors in the postsynaptic membrane of the intramural ganglia and the muscarinic receptors of the muscle. If the function of the postganglionic fibres is blocked by incubation of the muscle with tetrodotoxin, stimulation of the nicotinic receptors is prevented from contributing to

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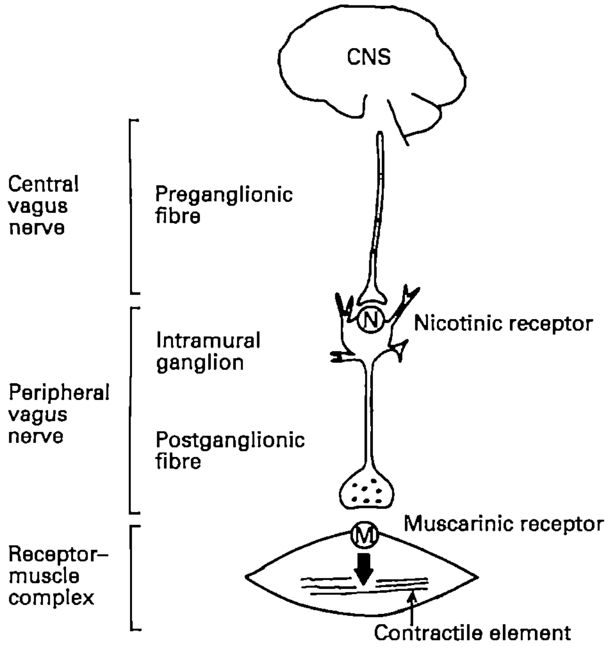

FIG. 1. Diagrammatic representation of vagal motor pathway. N = Postsynaptic nicotinic cholinergic receptor (site of action of DMPP); M = postjunctional muscarinic receptor (site of action of acetylcholine in the presence of tetrodotoxin). Thick black arrow represents chemical signal transmission. Electrical field stimulation acts on the postganglionic fibre since stimulation of the nicotinic receptors was blocked by hexamethonium.

the contractile response to acetylcholine. The contraction in response to acetylcholine in the presence of tetrodotoxin is therefore only caused by stimulation of the muscarinic receptors of the muscles. If the contractile response to acetylcholine in the presence of tetrodotoxin is reduced by ketamine, one may conclude that ketamine has a postjunctional effect—that is, it affects the muscarinic receptors, the chemical signal transmission from the receptors to the contractile elements, the contractile elements or a combination of the above. Our study was not designed to differentiate these intracellular events, and we refer to this postjunctional effect as an effect on the receptor–muscle complex.

Electrical field stimulation activates both the intramural ganglia and the postganglionic parasympathetic and sympathetic fibres. Stimulation of the ganglia and sympathetic fibres during electrical field stimulation was prevented from contributing to the contraction by incubation of the muscles with hexamethonium and propranolol, respectively. If the contractile response to electrical field stimulation in the presence of hexamethonium and propranolol is reduced by ketamine, one may conclude that ketamine affects the postganglionic fibres, the receptor–muscle complex, or both.

1-1-Dimethyl-4-phenyl-piperazinium (DMPP) stimulates the nicotinic receptors of the postsynaptic membrane of the ganglia. If the contractile response to DMPP is reduced in the presence of ketamine, ketamine may have an effect anywhere between the nicotinic receptors and the receptor–muscle complex.

MATERIALS AND METHODS

Tracheae from Large White adult pigs were obtained from a local abattoir and transported to the laboratory in cold (4 °C) pre-aerated physiological salt solution of the following composition (mmol litre^{-1}): 118.3 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1.2 $MgSO_4$, 1.2 KH_2PO_4, 25.0 $NaHCO_3$, 11.1 glucose. The tracheae were used within 3 h of the animal being killed, or were stored overnight at 4 °C in physiological salt solution aerated continuously with 5% carbon dioxide in oxygen. The epithelium and mucosa were stripped from the trachea and rectangular strips of trachealis muscle approximately 4 × 10 mm were dissected in aerated physiological salt solution. The muscle strips were suspended in 25-ml water-jacketed glass organ baths containing physiological salt solution at 37 °C and bubbled with 5% carbon dioxide in oxygen (pH 7.41–7.43, P_{CO_2} 4.5–4.7 kPa, P_{O_2} 57–59 kPa) (Instrumentation Laboratories). One end of the muscle strip was anchored to a fixed hook at the bottom of the bath and the other attached by a silk thread (3-0 Ethicon) to a force transducer (FTO3 Grass Medical Instruments) mounted on a micromanipulator that enabled the length of the strip to be changed. Isometric forces were recorded continuously (Grass Model 7 Polygraph).

The strips were washed regularly with physiological salt solution and stimulated by electrical field stimulation 0.5 ms, 25 Hz, 15 V for 30 s at approximately 5-min intervals (unpublished studies by us demonstrated that electrical field stimulation at these settings did not stimulate the porcine trachealis muscle directly). Electrical field stimulation was provided by a direct-current, square-wave pulse amplifier (Section of Engineering, Mayo Clinic) triggered by a stimulator (Model S44 Grass Medical Instruments) via two 1 × 4 cm parallel platinum electrodes located at either side of the strips. The muscle strips were stretched progressively over a period of 1–2 h until the response to electrical field stimulation was consistent and maximal. Each strip was then maintained at this optimal length throughout the experiment. The contractile response in all muscle strips to acetylcholine 10^{-4} mol litre^{-1} was determined and deemed the maximal response. After the maximal response had been achieved, the strips were washed repeatedly until they returned to their baseline force. The effect of ketamine was studied in two ways.

Effect of ketamine 10^{-4} mol litre^{-1} on concentration–response curves

We studied six tracheal muscle strips from each of six pigs. Two of the six strips from each pig were incubated with tetrodotoxin 10^{-6} mol litre^{-1} for 30 min before cumulative concentration–response curves to acetylcholine 10^{-9}–10^{-4} mol litre^{-1} (in half log molar increments) were obtained (fig. 2). The tetrodotoxin was added to prevent any contributing to the induced contraction as a result of stimulation by acetylcholine of muscarinic and nicotinic receptors in the intramural parasympathetic ganglia.

In two other of the six muscle strips from each pig, we obtained frequency–response curves to electrical

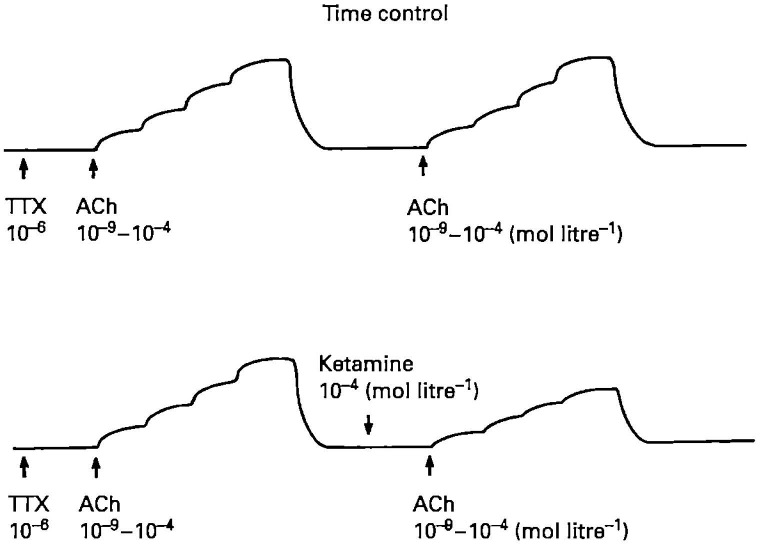

FIG. 2. Upper trace: Diagrammatic representation of two successive cumulative concentration–response curves to acetylcholine (ACh), forming a time control. Lower trace: Initial concentration–response curve to acetylcholine in the absence of ketamine, followed by incubation with ketamine 10^{-4} mol litre^{-1} and repetition of the acetylcholine concentration–response curve. TTX = Tetrodotoxin.

field stimulation (0.5 ms, 0.25–25 Hz, 15 V). Hexamethonium 10^{-5} mol litre^{-1} and propranolol 10^{-6} mol litre^{-1} were present in the bath for 30 min before and during the electrical field stimulation, to prevent stimulation of nicotinic cholinergic and beta-adrenoceptors, respectively.

In the remaining two of the six muscle strips from each pig, concentration–response curves to DMPP were obtained by adding DMPP non-cumulatively to the bathing solution to result in concentrations of 10^{-7}, 10^{-6}, 10^{-5} and 10^{-4} mol litre^{-1}. To avoid desensitization, DMPP was washed out immediately after the contractile response had reached a maximum (60 s from the time of administration of DMPP). Thirty minutes elapsed between each addition of DMPP.

After these initial measurements, the six strips were washed with physiological salt solution until they returned to their resting force. In one of each of the above three pairs of muscle strips, ketamine 10^{-4} mol litre^{-1} (racemate) was added to the baths; the other three strips served as controls for the effect of time. After 30 min, a second complete set of measurements in response to acetylcholine (fig. 2), electrical field stimulation and DMPP was obtained in all muscle strips.

Effect of ketamine on precontracted muscles

Four muscle strips from each of another six pigs were contracted with acetylcholine 4.1 (SD 3.4) × 10^{-6} mol litre^{-1} to 50.4 (9.1) % of their maximal response to acetylcholine 10^{-4} mol litre^{-1}. One of the four precontracted strips had no further drugs added, thereby acting as a time control. Cumulative concentration–response curves to ketamine 10^{-7}–$10^{-3.5}$ mol litre^{-1} (in half log molar increments) were obtained in the three remaining precontracted strips, one strip having been incubated for 30 min with tetrodotoxin 10^{-6} mol litre^{-1}, and another incubated for 30 min with propranolol 10^{-6} mol litre^{-1} (fig. 3).

Four muscle strips from each of another six pigs were exposed to potassium chloride 63 mmol litre^{-1}-substituted physiological salt solution (potassium chloride substituted for sodium chloride on an equimolar basis) to determine the maximal response to potassium chloride [10]. Thereafter, the muscle strips were washed repeatedly until they returned to resting force, and they were then precontracted to 52.9 (5.1) % of this maximal response (EC_{50}) with isotonic potassium chloride 27.2 (4.8) mmol litre^{-1}-substituted physiological salt solution. In one of the four precontracted strips from each pig, a concentration–response curve to ketamine 10^{-7}–$10^{-3.5}$ mol litre^{-1} (in half log molar increments) was obtained; a second precontracted muscle strip from each pig served as a time control. The third and fourth precontracted muscle strips from four of the six pigs were incubated with atropine 10^{-6} mol litre^{-1} for 30 min before contracting them with potassium chloride 29.8 (3.3) mmol litre^{-1} to their EC_{50} (49.5 (11.8) % of maximal response). In the third muscle strip, a ketamine concentration–response curve was obtained; the fourth muscle strip served as a time control.

At the end of the experiments all strips were blotted dry and weighed after excess tissue had been removed. They were fixed in glutaraldehyde, cut in 1-μm sections and stained with toluidine blue. The entire experiment took approximately 5 h to complete and the results from all muscle strips are included.

Data analysis

The contractile muscle responses were adjusted for the effect of time according to the formula:

$$Ct = (C2/C1) \times Ck$$

where Ct = time-adjusted control response from ketamine muscle; C1 = response of control muscle (initial measurement); C2 = response of control

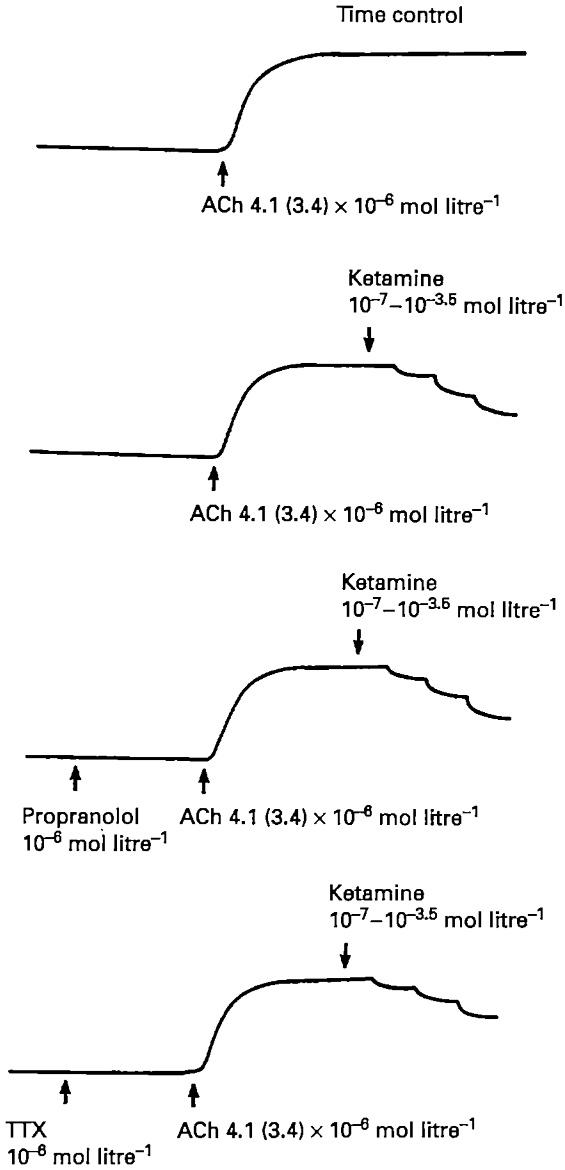

FIG. 3. Upper trace: Diagrammatic representation of the acetylcholine-induced contraction (ACh), which acts as a time control. Second trace: Concentration–response curve to ketamine in a muscle precontracted with acetylcholine. Third trace: Concentration–response curve to ketamine in a muscle precontracted with acetylcholine and preincubated with propranolol 10^{-6} mol litre^{-1}. Fourth trace: Concentration–response curve to ketamine in a muscle precontracted with acetylcholine and preincubated with tetrodotoxin (TTX) 10^{-6} mol litre^{-1}.

muscle (measured in parallel with ketamine muscle); Ck = response of ketamine muscle (initial measurement before exposure to ketamine).

Similarly, in precontracted muscles exposed to varying concentrations of ketamine, we calculated the time-adjusted responses. We compared concentration response curves by repeated measures analysis of variance.

The effects of ketamine on contractions induced by DMPP, acetylcholine or electrical field stimulation were compared. The concentration of DMPP producing 20% of the maximal contraction to acetylcholine was determined. (This force was used because it was achieved by all muscle strips exposed to DMPP 10^{-4} mol litre^{-1}.) The contractile response in the presence of ketamine at this concentration of DMPP was obtained next and the reduction in contractile response attributable to ketamine calculated. The same procedure was observed for concentration–response curves to acetylcholine and the frequency–response curves to electrical field stimulation.

Statistical differences in the mean reductions in contractile response to DMPP, acetylcholine and electrical field stimulation were examined by paired two-tailed *t* test. Concentration–response curves to acetylcholine in fresh and stored tracheae were compared with repeated measures analysis of variance. Data are expressed as mean (SD). $P < 0.05$ was considered significant. In all cases *n* indicates the number of pigs and not the number of muscle strips studied.

Drugs and chemicals were obtained from Sigma Chemical Company: acetylcholine chloride, ketamine hydrochloride, 1,1-dimethyl-4-phenylpiperazinium iodide, propranolol hydrochloride, tetrodotoxin, hexamethonium chloride, atropine sulphate. Drugs were added to the physiological salt solution in 100-μl aliquots. Concentrations are expressed as the final molar concentration in the organ bath.

RESULTS

Histological examination showed that removal of epithelium and mucosa was complete. There was no difference in the maximal force of the stored and fresh muscles ($P = 0.84$). There were no significant differences in weight and resting force of the muscles exposed to acetylcholine, electrical field stimulation, DMPP and potassium chloride (table I). The maximal force developed in response to DMPP was significantly less than that with acetylcholine, electrical field stimulation or potassium chloride ($P < 0.01$).

Effect of ketamine 10^{-4} mol litre^{-1} on concentration–response curves

Ketamine had no effect on resting force. It caused a shift to the right in the acetylcholine concentration–response curve ($P < 0.02$) (fig. 4A). Similarly, the frequency–response curve to electrical field stimulation was shifted significantly to the right by ketamine ($P < 0.001$) (fig. 4B). No response to DMPP was obtained in the presence of ketamine 10^{-4} mol litre^{-1} ($P < 0.02$) (fig. 4C).

The effect of ketamine 10^{-4} mol litre^{-1} was compared on muscles contracted with acetylcholine, electrical field stimulation or DMPP to 20% of the

TABLE I. *Weight, resting and maximal force in muscles exposed to various stimuli (mean (SD); n = 6). ACh = acetylcholine; EFS = electrical field stimulation; DMPP = dimethyl-phenyl-piperazinium; KCl = potassium chloride. *Significantly different from ACh, EFS and KCl (P < 0.01).*

Stimulus	Weight (mg)	Resting force (g)	Maximal force (g)
ACh	23.0 (5.4)	0.6 (0.5)	10.1 (5.4)
EFS	20.4 (8.2)	0.8 (0.9)	9.4 (4.5)
DMPP	18.8 (6.5)	0.8 (0.7)	2.8 (2.5)*
KCl	21.0 (6.4)	1.0 (0.9)	9.4 (4.4)

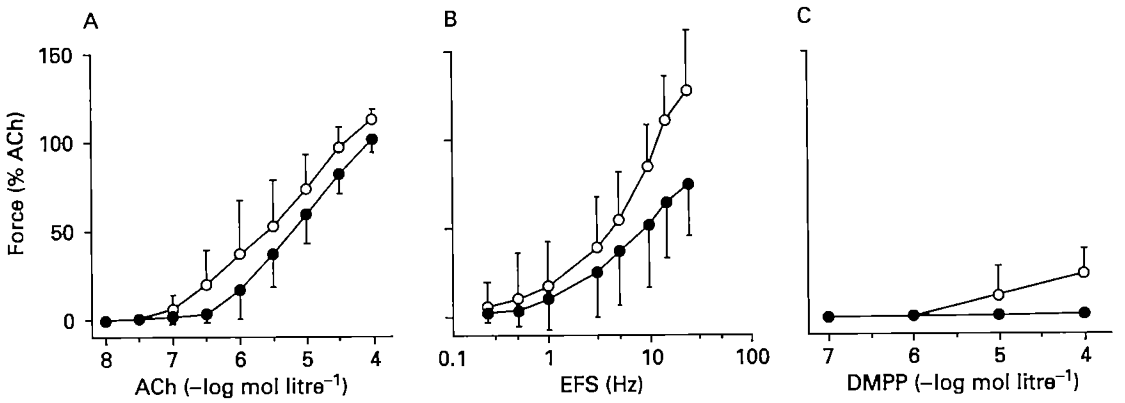

FIG. 4. Concentration–response curves to (A) acetylcholine (ACh), (B) electrical field stimulation (EFS) and (C) dimethyl-phenyl-piperazinium (DMPP) in isolated pig trachealis muscle strips in the absence (control) (○) and presence of ketamine 10^{-4} mol litre^{-1} (●). Force = mean (SD) percentage of the response to acetylcholine 10^{-4} mol litre^{-1}.

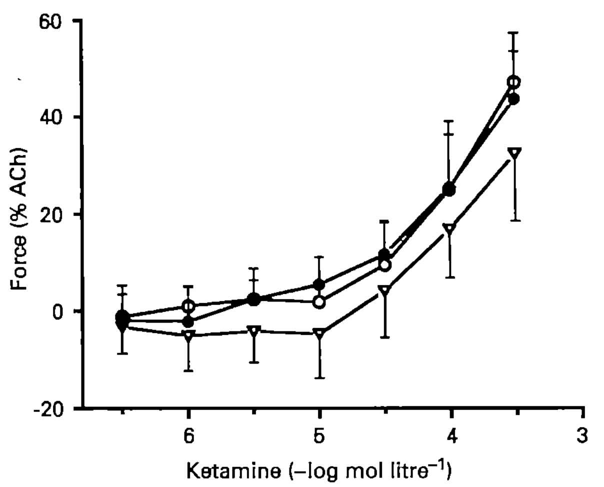

FIG. 5. Concentration–response curves to ketamine in isolated pig trachealis muscle strips contracted to EC_{50} with acetylcholine (ACh) (control) (○) and preincubated with propranolol 10^{-6} mol litre^{-1} (●) or tetrodotoxin (TTX) 10^{-6} mol litre^{-1} (▽). Force = mean (SD) percentage relaxation from the acetylcholine-induced contraction.

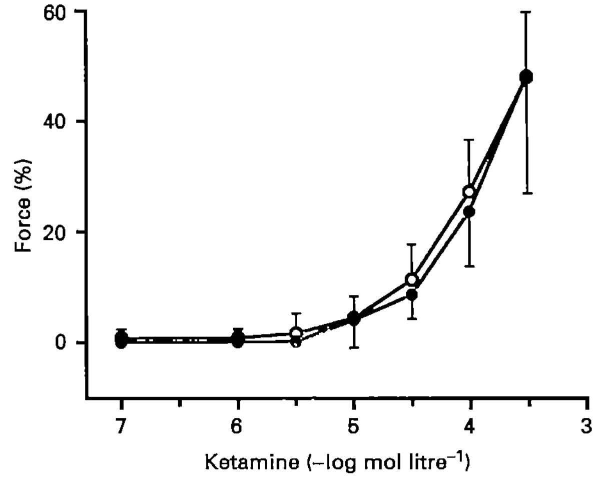

FIG. 6. Concentration–response curves to ketamine in isolated pig trachealis muscle strips contracted to EC_{50} with potassium chloride (KCl) in the absence of atropine (control; $n = 6$) (○) and in the presence of atropine 10^{-6} mol litre^{-1} ($n = 4$) (●). Force = mean (SD) percentage relaxation from KCl-induced contraction.

maximal force achieved with acetylcholine 10^{-4} mol litre^{-1}. This amount of force was produced, in the absence of ketamine, by acetylcholine 0.9 (0.8) × 10^{-6} mol litre^{-1}, 2.6 (2.0)-Hz electrical field stimulation and DMPP 6 (5) × 10^{-5} mol litre^{-1}. In the presence of ketamine 10^{-4} mol litre^{-1}, the force of contraction produced by these stimuli decreased by 68.3 (24.2) % for the muscles stimulated with acetylcholine, by 71.6 (16.6) % for muscles stimulated with electrical field stimulation and by 100 % (no contraction at all) for muscles stimulated with DMPP ($P < 0.05$ for acetylcholine and electrical field stimulation *vs* DMPP; $P = 0.87$ for acetylcholine *vs* electrical field stimulation).

Effect of ketamine on precontracted muscles

In muscles precontracted with acetylcholine to 50.4 (9.1) % of their maximal response to acetylcholine 10^{-4} mol litre^{-1}, ketamine caused a concentration-dependent relaxation. This was unaffected by propranolol 10^{-6} mol litre^{-1} ($P = 0.94$). Tetrodotoxin 10^{-6} mol litre^{-1} decreased significantly ($P < 0.05$) the maximal relaxation obtained with ketamine $10^{-3.5}$ mol litre^{-1}, from 46.7 (10.2) % to 32 (13.8) %. The shift of the concentration–response curve, however, was not statistically significant ($P = 0.06$) (fig. 5).

In muscles precontracted with potassium chloride to 52.9 (5.1) % of their maximal response to potassium chloride 63 mmol litre^{-1}, ketamine caused a concentration-dependent relaxation (fig. 6), which was not significantly different from that in muscle strips precontracted with acetylcholine ($P = 0.97$).

In muscle strips incubated with atropine 10^{-6} mol litre^{-1} and contracted with potassium chloride to 49.5 (11.8) % of their maximal response, ketamine caused a concentration-dependent relaxation which did not differ from that in the absence of atropine ($P = 0.54$) (fig. 6) or from that in muscles precontracted with acetylcholine ($P = 0.85$).

DISCUSSION

This study has shown that ketamine attenuated contraction of isolated porcine trachealis muscle at two sites along the peripheral vagus nerve motor pathway, depressing the contractile response of the smooth muscle to acetylcholine and the excitability of the postsynaptic nicotinic cholinergic receptors of the intramural parasympathetic ganglion. Ketamine relaxed porcine trachealis muscle precontracted with either acetylcholine or potassium chloride, suggesting that the relaxant action of ketamine is not dependent on an effect on the muscarinic receptors.

Choice of stimuli

We studied the effect of ketamine on the contractile response to DMPP, electrical field stimulation and acetylcholine to determine the site of action of ketamine on the peripheral vagus nerve (fig. 1). DMPP was used to stimulate nicotinic cholinergic receptors in the intramural ganglia [11].

Electrical field stimulation stimulates pre- and postganglionic parasympathetic, sympathetic and non-adrenergic non-cholinergic nerve fibres, and smooth muscle directly. Stimulation of nicotinic cholinergic receptors and beta adrenoceptors was blocked by hexamethonium and propranolol, respectively. Activation of smooth muscle by electrical field stimulation did not occur in our study, because no contraction in response to electrical field stimulation was observed after the muscles had been incubated with tetrodotoxin. In porcine trachealis muscle, non-adrenergic–non-cholinergic neurotransmission is mediated by nitric oxide [12]. Inhibition of nitric oxide formation by L-nitroarginine does not affect the relaxation by ketamine of intact guineapig tracheal muscle precontracted with carbachol [13]. This suggests that non-adrenergic–non-cholinergic innervation is unlikely to play a major role in the relaxation produced by ketamine. We conclude that electrical field stimulation in our study effectively stimulated both the postganglionic parasympathetic and the non-adrenergic–non-cholinergic nerve fibres.

During stimulation of the muscle with acetylcholine, tetrodotoxin prevented transmission of any ganglionic stimulation by acetylcholine from contributing to the response. Contraction of the muscle by acetylcholine was, therefore, the result of stimulation only of the muscarinic receptors at the smooth muscle.

In summary, in this study DMPP initiated contraction by stimulating postsynaptic nicotinic receptors of the intramural ganglia, electrical field stimulation activated the postganglionic cholinergic nerve and non-adrenergic–non-cholinergic fibres and acetylcholine stimulated the muscarinic receptors on the smooth muscle. If ketamine caused relaxation by an interaction at each of these three sites (receptor–muscle complex, postganglionic cholinergic nerve fibre and intramural ganglion), one would expect the least depression of force to occur with acetylcholine-induced contraction (with which ketamine could interact only with the muscle–receptor complex); greater depression of force with electrical field stimulation-induced contraction (ketamine interacting with nerve and muscle–receptor complex); and the greatest reduction in force to occur with DMPP-induced contraction (ketamine interacting with the intramural ganglion, nerve and muscle–receptor complex).

Action of ketamine 10^{-4} mol litre^{-1} on concentration–response curves

The rightward shift of the concentration–response curve to acetylcholine and the frequency–response curve to electrical field stimulation indicates that in the presence of ketamine a larger stimulus is required to produce the same degree of contraction. The depression of the response to acetylcholine by ketamine 10^{-4} mol litre^{-1} demonstrates an effect of ketamine on the muscarinic receptor–muscle complex. The depression of force by ketamine 10^{-4} mol litre^{-1}, in muscles contracted to the same force by electrical field stimulation, was similar in magnitude to that in muscles contracted with acetylcholine. This suggests no additional effect of ketamine on neural transmission in the postganglionic cholinergic nerves. The abolition, by ketamine 10^{-4} mol litre^{-1}, of contractions caused by DMPP indicates an additional depressant effect on the postganglionic nicotinic cholinergic receptors in the intramural ganglion. Similar effects have been shown with halothane, enflurane and isoflurane in canine trachealis smooth muscle—namely, a decrease in the excitability of the postsynaptic nicotinic receptors of the intramural parasympathetic ganglion and an effect on the smooth muscle–receptor complex [14].

The conclusion that ketamine decreased the excitability of the intramural parasympathetic ganglion is supported further by the observation that tetrodotoxin decreased the concentration-dependent relaxation by ketamine of muscles precontracted with acetylcholine (fig. 5).

Effect of ketamine on precontracted muscles

It is of interest to study the effect of drugs on both initiation and maintenance of contraction of airway smooth muscle as different intracellular events are involved. Initiation of contraction (cross-bridge formation) by muscarinic agonists is associated with release of calcium from the sarcoplasmic reticulum by inositol 1,4,5 triphosphate and a subsequent large intracellular concentration of calcium [15]. In contrast, in the maintenance of contraction (latch-bridge formation) the sensitivity of the contractile proteins may be altered by diacylglycerol [16] so that contraction is maintained in the presence of smaller intracellular calcium concentrations. It is possible, therefore, for a drug to have a different effect on initiation of contraction than on maintenance of contraction.

In the concentration–response curve studies, ketamine was present during the initiation of contraction and subsequent maintenance of contraction, whereas in the studies on precontracted muscles, ketamine was present during the maintenance of contraction only. We found that in both cases ketamine had a relaxing effect. If ketamine had an effect only on initiation of contraction, no relaxation would be seen in the precontracted muscles when exposed to ketamine. However, as relaxation occurred in both the concentration–response curve studies and the precontracted muscle studies, we cannot separate the effects of ketamine on initiation and maintenance of contraction.

The relaxant effect of ketamine was similar in muscle strips contracted with potassium chloride and acetylcholine. Potassium causes contraction by membrane depolarization and activation of voltage-dependent calcium channels, resulting in an increased trans-sarcolemmal flux of calcium [17]. It may also cause acetylcholine release by depolarization of postganglionic parasympathetic nerve terminals [18]. The elimination of any contribution of released acetylcholine to the contraction by incubation with atropine did not alter the concentration–response curve to ketamine. We conclude that ketamine may affect an intracellular pathway common to potassium chloride and acetylcholine.

Beta adrenoceptor activation is known to cause relaxation of airway smooth muscle [19]. In this *in vitro* study, propranolol had no effect on ketamine-induced relaxations. In contrast, *in vivo* propranolol blocks the protective effect of ketamine against bronchospasm in ascaris-sensitized dogs [8]. The absence of neural and hormonal effects *in vitro* probably account for this difference.

Limitations

Only the peripheral component of the vagus nerve was studied; the hormonal and central neural control mechanisms of the trachealis muscle were not examined. The effect of ketamine on the non-adrenergic–non-cholinergic innervation was not examined.

In our study, the epithelium was removed from the preparation. The modulatory role of the epithelium and the effect of the putative epithelium-derived relaxing factor [20, 21] on ketamine-induced relaxation is unknown. Both fresh and stored muscles were studied, but no difference was found in the contractile response to acetylcholine.

Clinical implication

The ability of ketamine to relax smooth muscle independent of the agonists used to induce tone parallels the success of ketamine clinically as a bronchodilating agent in asthmatic patients. The lack of effect of ketamine on baseline force emphasizes the need to consider intrinsic airway smooth muscle tone when clinically assessing the effect of bronchodilating agents. Although comparison between *in vitro* and *in vivo* drug concentrations across species is of limited value, it is of interest to note that an *in vitro* effect in this study was found with concentrations occurring in clinical practice (2.5×10^{-6}–6×10^{-5} mol litre^{-1}) [22].

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SEVOFLURANE DOES NOT INCREASE INTRACRANIAL PRESSURE IN HYPERVENTILATED DOGS

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SUMMARY

We have measured the effects of 0.5, 1.0 and 1.5 MAC (minimum alveolar concentration) end-tidal concentrations of sevoflurane on intracranial pressure (ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP), central venous pressure and heart rate in hypocapnic dogs (Pa_{CO_2} 3.2–3.7 kPa) and compared the data with those produced by equi-MAC concentrations of enflurane and halothane. Enflurane and halothane caused small but significant increases in ICP at 0.5, 1.0 and 1.5 MAC, but there were no changes with sevoflurane. However, sevoflurane caused a considerable decrease in MAP with consequent decrease in CPP. We conclude that sevoflurane should be a suitable agent for neuroanaesthesia and is preferable to either enflurane or halothane. (Br. J. Anaesth. 1993; **71**: 551–555)

KEY WORDS

Anaesthetic, volatile: sevoflurane. Brain: intracranial pressure, cerebral perfusion pressure. Carbon dioxide: hypocapnia, normocapnia.

Sevoflurane is a volatile anaesthetic with a relatively low blood:gas partition coefficient of 0.63, compared with 1.90 and 2.40 for enflurane and halothane, respectively [1]. It has a pleasant, non-pungent odour, which permits smooth and rapid inhalation induction. It should be suitable, therefore, for neurosurgical patients, in whom rapid induction and recovery are often desired. Sevoflurane is an ether anaesthetic and there is some concern that it may induce seizure activity, in common with enflurane [2], particularly in the presence of hypocapnia. However, it was not found to induce seizure activity in dogs at 1.5, 2.0 and 2.5 MAC during normocapnia or hypocapnia, even in the presence of intense auditory stimuli [3]. Scheller and colleagues found that the effects of sevoflurane on cerebral blood flow (CBF), cerebral metabolic rate for oxygen ($CMRo_2$), intracranial pressure (ICP) and the EEG were similar to those of isoflurane in normocapnic rabbits [4]. However, its effects on ICP and cerebral perfusion pressure (CPP) during hypocapnia have not been studied. We have therefore compared the effects of sevoflurane, enflurane and halothane on ICP, CPP and the cardiovascular system in hypocapnic dogs.

MATERIAL AND METHODS

This study was approved by The Animal Care and Use Committee at the Hamamatsu University School of Medicine. We studied 24 unmedicated mongrel dogs (weights 5–12 kg). Anaesthesia was induced with sodium pentobarbitone 30 mg kg^{-1} and pancuronium 0.2 mg kg^{-1}. The trachea was intubated and the lungs ventilated with 60% nitrous oxide in oxygen; Pa_{CO_2} was maintained in the normal range (4.9–5.3 kPa). The animals were placed in the supine position and the right femoral artery was cannulated for measurement of arterial pressure and blood sampling. The right external jugular vein was cannulated for measurement of central venous pressure (CVP) and administration of fluids and drugs.

Surgical preparation was carried out in all cases after local infiltration of 0.25% bupivacaine.

A burr hole 10 mm in diameter was drilled in the right parietal area and a small catheter was inserted into the subdural space for measurement of ICP. A drop of cyanocrylate cement was used to seal the dura.

Measured variables included mean arterial pressure (MAP), heart rate (HR), CVP, ICP, end-tidal concentrations of volatile anaesthetic (measured at the distal end of endotracheal tube), carbon dioxide and oxygen, and arterial blood-gas tensions. CPP was calculated as the difference between MAP and ICP (at the level of the head).

End-tidal concentrations of carbon dioxide and volatile anaesthetic were recorded using a mass spectrometer (Perkin–Elmer MGA 1100; Perkin-Elmer, Pomano, CA). Rectal temperature was maintained at 36.5–37.5 °C with a heating blanket. Ringer lactate solution was infused i.v. at 5 ml kg^{-1} h^{-1}.

The animals were left undisturbed for 30 min before baseline (control) measurements were made, with Pa_{CO_2} maintained at normocapnia. Hyperventilation was induced by increasing the rate of ventilation and Pa_{CO_2} was maintained at 3.2–3.7 kPa for at least 15 min. The animals were then allocated randomly to receive halothane ($n = 8$), enflurane (n

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TABLE I. *Mean* (SEM) *intracranial pressure (ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP) and volatile anaesthetic concentrations (S = sevoflurane; E = enflurane; H = halothane). Normocapnia = arterial carbon dioxide tension 4.9–5.3 kPa; hypocapnia = arterial carbon dioxide tension 3.2–3.7 kPa. Significantly different from control values:* *$P < 0.05$; **$P < 0.01$. *Significantly different from sevoflurane values:* †$P < 0.05$; ††$P < 0.01$

	Normocapnia, control			Hypocapnia, pre-exposure			Hypocapnia, 0.5 MAC		
	S	E	H	S	E	H	S	E	H
ICP (mm Hg)	5.1 (0.7)	6.6 (0.7)	7.6 (0.7)	3.8 (0.7)	5.0 (0.3)	5.6 (0.4)	5.0 (0.9)	10.3 (1.0)**†	12.0 (1.4)**††
CPP (mm Hg)	120 (5)	125 (8)	118 (5)	119 (7)	128 (6)	122 (6)	105 (7)*	62 (5)**	92 (6)**
MAP (mm Hg)	125 (5)	131 (8)	125 (5)	123 (6)	133 (6)	128 (5)	110 (6)*	93 (6)**	104 (5)**
	Hypocapnia, 1.0 MAC			**Hypocapnia, 1.5 MAC**			**Hypocapnia, post-exposure**		
	S	E	H	S	E	H	S	E	H
ICP (mm Hg)	5.6 (1.2)	10.6 (0.6)**†	12.0 (1.2)**††	6.4 (1.4)	10.0 (0.8)**	11.8 (1.1)**†	5.3 (0.9)	7.8 (0.8)	8.8 (0.8)†
CPP (mm Hg)	88 (6)**	57 (5)**††	73 (5)**	68 (5)**	38 (4)**††	59 (5)**	112 (11)	111 (8)	102 (5)*
MAP (mm Hg)	95 (5)**	68 (5)**††	85 (5)**	75 (4)**	48 (5)**††	68 (4)**	117 (10)	119 (8)	111 (5)*

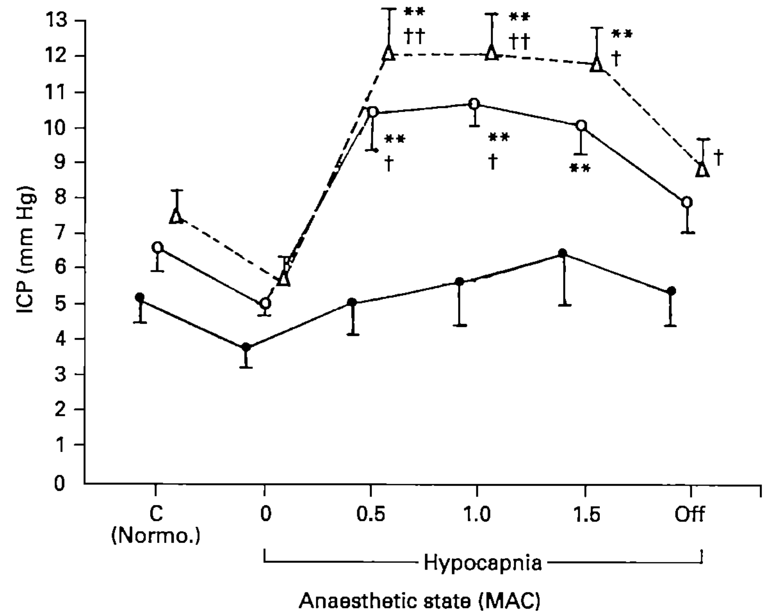

FIG. 1. Mean (SEM) changes in intracranial pressure (ICP) with sevoflurane (●), enflurane (○) or halothane (△). **$P < 0.01$ compared with control. †$P < 0.05$, ††$P < 0.01$ compared with sevoflurane. Normo. = normocapnia.

= 8) or sevoflurane ($n = 8$) (one volatile anaesthetic per animal), administered at 0.5 MAC end-tidal concentration. Measurements of variables were repeated 15 min later. The end-tidal concentration of the anaesthetic was increased to 1.0 MAC and 1.5 MAC for at least 15 min and all measurements repeated. The volatile anaesthetic was then discontinued. Twenty minutes later, all measurements were repeated using only a background anaesthetic of nitrous oxide.

MAC values were: sevoflurane 2.36 %, enflurane 2.2 %, halothane 0.89 % [5].

Statistical analysis

All data were expressed as mean (SEM). pH, Pa_{CO_2}, Pa_{O_2}, ICP, CPP, MAP, HR and CVP were compared within groups at the six anaesthetic states using a repeated measures analysis of variance followed by Dunnett's test [6] (comparison with control) where appropriate. pH, Pa_{CO_2}, Pa_{O_2}, ICP, CPP, MAP, HR and CVP were compared between the three anaesthetic agents at comparable MAC values by analysis of variance and, where differences were detected, pair-wise comparisons (sevoflurane with enflurane, sevoflurane with halothane) were performed using Student's t test for unpaired data with the Bonferroni correction for multiple comparisons. Changes were considered significant at $P < 0.05$.

RESULTS

ICP, CPP and MAP data are shown in table I. There were no intergroup differences in mean Pa_{CO_2}, Pa_{O_2} and pH values at which ICP, CPP, MAP, HR and

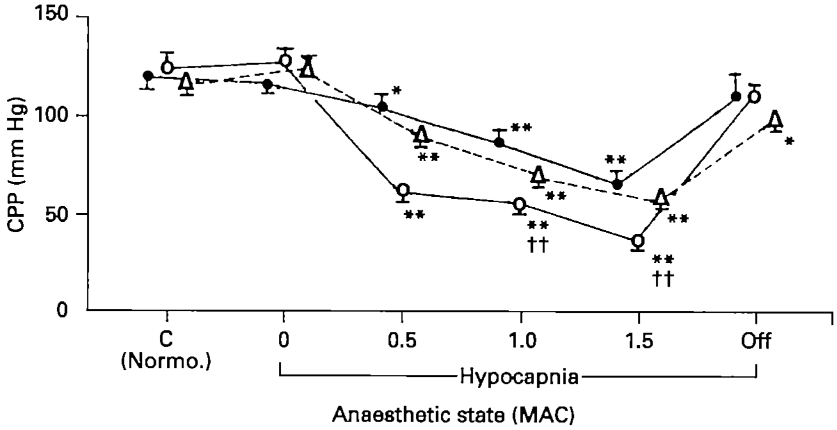

FIG. 2. Mean (SEM) changes in cerebral perfusion pressure (CPP) with sevoflurane (●), enflurane (○) or halothane (△). *$P < 0.05$, **$P < 0.01$ compared with control. ††$P < 0.01$ compared with sevoflurane. Normo. = normocapnia.

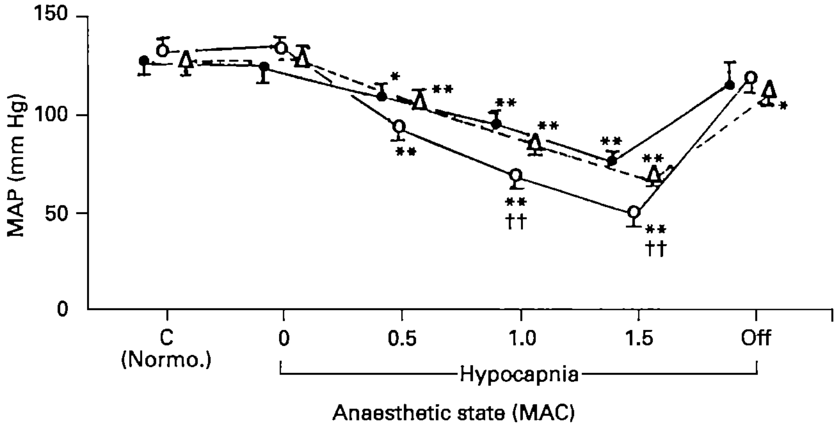

FIG. 3. Mean (SEM) changes in mean arterial pressure (MAP) with sevoflurane (●), enflurane (○) or halothane (△). *$P < 0.05$, **$P < 0.01$ compared with control. ††$P < 0.01$ compared with sevoflurane. Normo. = normocapnia.

CVP were compared: hyperventilation had no significant effect on Pa_{O_2}, which remained in the range 24.7 (2.4)–28.8 (2.0) kPa, but caused pH to increase to 7.43 (0.01)–7.49 (0.03) and Pa_{CO_2} to decrease to 3.2 (0.4)–3.7 (0.1) kPa.

There were no intergroup differences in ICP before administration of volatile agents. ICP increased significantly with 0.5, 1.0 and 1.5 MAC enflurane and halothane, but not with sevoflurane in any anaesthetic concentration (fig. 1). After discontinuation of the volatile anaesthetic, ICP remained significantly greater in the halothane than in the sevoflurane group.

Hyperventilation caused no change in CPP or MAP. Addition of the volatile anaesthetics caused a significant decrease in CPP (fig. 2) and MAP (fig. 3). There was no difference in the rate of decrease in arterial pressure with all three agents. In the sevoflurane and enflurane groups, CPP and MAP returned to the initial baseline values after discontinuation of the volatile anaesthetic. In the halothane group, CPP and MAP did not return to control values.

There were no intergroup differences in HR and CVP at any anaesthetic level. Hyperventilation had no significant effect on HR, which ranged from 152 to 169 beat min^{-1}, or CVP (1.4–2.1 mm Hg). HR decreased significantly with 1.0 and 1.5 MAC of sevoflurane and halothane, and 0.5, 1.0 and 1.5 MAC of enflurane.

DISCUSSION

During halothane anaesthesia, the vasoconstrictor effect of hypocapnia exceeds the vasodilator effects of the volatile anaesthetic [7]. When hypocapnia (Pa_{CO_2} less than 4 kPa at normothermia) is produced in patients with intracranial lesions, the effects of subsequent administration of 0.5–1.0% halothane on ICP are consistently blocked. However, simultaneous administration of hyperventilation and halothane does not always prevent a large increase in ICP [7]. Although enflurane is a less potent cerebral vasodilator than halothane, it has been shown to increase CBF [2] and ICP [8, 9] in both animals and humans. Enflurane may be used for patients with intracranial pathology if hypocapnia is induced before its administration [10]. Isoflurane is the least potent cerebral vasodilator compared with enflurane or halothane and thus has least effect on CBF [11, 12] and ICP [13, 14]. Although isoflurane causes an increase in ICP in patients with intracranial space-occupying lesions, in contrast with halothane, it is not necessary to establish hypocapnia before administration of the drug [13]. Isoflurane and sevoflurane are comparable in their capacities to increase ICP in normocapnic rabbits [4]. The response of canine cerebral circulation to hyperventilation during anaesthesia with sevoflurane has not been examined.

In this study, we have shown that enflurane and halothane caused significant increases in ICP at 0.5, 1.0 and 1.5 MAC despite prior establishment of hypocapnia, while sevoflurane had no effect in any concentration. These data for halothane and enflurane conflict with those reported previously [7, 10]. There are several explanations for these discrepancies.

First, the present study was conducted in dogs with normal intracranial compliance, but one previous study [7] was performed on humans with supratentorial mass lesions. Second, in that study [7], measurement of ICP was made, not in the intracranial space, but in the lumbar subarachnoid space. Third, as the authors did not measure the end-tidal concentration of halothane, it is likely that their patients received halothane in concentrations less than 1.2 MAC.

Previous studies have reported an increase in ICP in rabbits [4] and dogs [3] after administration of sevoflurane. In common with isoflurane, sevoflurane has been shown to have minimal effect on CBF [3, 4]. Its effects of ICP in our study were essentially the same as those reported for isoflurane [13]. Isoflurane may cause a dose-related increase in CBF [15] accompanied by an increase in ICP [16], both of which may be attenuated by hyperventilation [17].

ICP increases in response to changes in either CBF or cerebrospinal fluid (CSF) volume. The effects of sevoflurane on CBF have been reported, but effects on cerebral blood volume (CBV) and CSF dynamics remain unclear. During isoflurane anaesthesia, hyperventilation decreases CBV, resulting in decreased ICP. Although CBV gradually increases with exposure to isoflurane, this change is opposed by a decrease in CSF volume; thus there is no net increase in ICP [18]. In contrast with enflurane [19], isoflurane has no significant effect on rate of production of CSF [20] and decreases resistance to the reabsorption of CSF in the dog. Hyperventilation apparently has no significant effect on this particular component of ICP [21].

Our study has shown that all three volatile agents caused significant decreases in MAP and CPP with increasing anaesthetic concentrations. There was no difference in the rate of change in arterial pressure with the three agents. The increase in ICP with enflurane and halothane commenced before the arterial pressure decrease and thus we believe the increase in ICP with these two agents was caused by a direct vasodilatation of cerebral vessels. With 1.0 and 1.5 MAC enflurane anaesthesia, MAP decreased markedly compared with sevoflurane and CPP consequently decreased to less than 50 mm Hg (figs 2, 3), the lower end of the autoregulatory range. Thus it is possible that small concentrations of inhalation anaesthetics may be used safely during anaesthesia for intracranial operation on patients with brain tumours, provided that arterial pressure is monitored carefully. The effects of these agents on MAP may facilitate control of arterial pressure and the induction of hypotension during neurosurgery.

It should be emphasized that our study was conducted in dogs with normal brains and the data may not be applicable to animals or patients with intracranial disease.

We used three inhalation anaesthetics in the presence of nitrous oxide and pentobarbitone. The former is a cerebral vasodilator that increases CBV and ICP [22–24] and its use (along with local anaesthetic infiltration of all wounds) represents a compromise between essential analgesia in the control state and minimal cerebrovascular effects. The effects of nitrous oxide on ICP may be attenuated by prior administration of pentobarbitone and hypocapnia [22].

We have shown that sevoflurane caused a dose-dependent decrease in arterial pressure and HR during hypocapnia as has been observed in normocapnic dogs [25, 26]. The decrease in arterial pressure results from a decrease in systemic vascular resistance rather than in cardiac output [3].

If the cerebral circulation of anaesthetized humans responds in the same manner as that of the dog, we conclude that sevoflurane should not increase ICP during established hypocapnia, in contrast with halothane and enflurane. During neurosurgery, therefore, if arterial pressure is monitored carefully, sevoflurane should serve as a suitable agent and is preferable to halothane or enflurane, both of which may cause undesirable increases in ICP.

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ISOBOLOGRAPHIC AND DOSE–RESPONSE ANALYSIS OF THE INTERACTION BETWEEN PIPECURONIUM AND VECURONIUM†

M. NAGUIB AND M. ABDULATIF

SUMMARY

We have studied the neuromuscular effects of pipecuronium, vecuronium and their combination in 130 ASA group I or II patients. Patients were anaesthetized with 0.8% halothane and 60% nitrous oxide in oxygen. Neuromuscular block was recorded as the evoked thenar mechanomyographic response to train-of-four stimulation of the ulnar nerve (2 Hz at 10-s intervals). The dose–response curves were determined by probit analysis. The calculated doses producing 50% depression of the first twitch height were 15.6, 16.9 and 15.0 μg kg^{-1} for the pipecuronium, vecuronium and pipecuronium–vecuronium combination groups, respectively. Isobolographic and algebraic (fractional) analyses were used to assess quantitatively the combined neuromuscular effect of pipecuronium and vecuronium and to define the type of interaction between these drugs. The interaction between pipecuronium and vecuronium was found to be additive. (Br. J. Anaesth. 1993; **71**: 556–560)

KEY WORDS

Interactions (drug): pipecuronium, vecuronium. Neuromuscular relaxants: pipecuronium, vecuronium. Potency: ED_{50}.

Pipecuronium bromide is a long-acting, non-depolarizing neuromuscular blocking agent that is structurally similar to pancuronium and vecuronium. Pipecuronium has a bisquaternary structure with piperazine rings attached at positions 2 and 16 of the steroid nucleus. Vecuronium, which is the 2β monoquaternary analogue of pancuronium, is a relatively shorter-acting compound.

Several studies have indicated that non-depolarizing neuromuscular synergy occurred for combinations of chemically unrelated compounds such as tubocurarine and gallamine [1, 2], pancuronium and di-methyl tubocurarine [3] or pancuronium and tubocurarine [3, 4]. Others, however, demonstrated an additive interaction of gallamine with tubocurarine or pancuronium combinations [5–7]. In common with pancuronium, vecuronium exhibited synergy when combined with tubocurarine in humans [8]. Although the precise mechanisms underlying synergistic interaction are not known, it was proposed that synergy was related to the action of non-depolarizing neuromuscular blocking agents at multiple receptor sites at the neuromuscular junction [3, 4, 8]. Nevertheless, none of the data from the aforementioned studies were subjected to standard drug–drug interaction analysis, for example by isobolographic analysis.

Combinations of pipecuronium and vecuronium have not been studied *in vivo* before. The present study was undertaken to characterize the interaction of pipecuronium and vecuronium combination in humans.

PATIENTS AND METHODS

After obtaining institutional approval and informed consent, we studied 130 ASA group I or II adult patients (65 male). All were undergoing elective procedures, had no neuromuscular, renal or hepatic disease, and were not taking any drug known to interfere with neuromuscular function. All patients were premedicated with diazepam 10 mg orally approximately 90 min before induction of anaesthesia. An i.v. infusion of lactated Ringer's solution was commenced before induction of anaesthesia. Routine monitoring was used. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5 ± 0.5 °C.

In all patients, anaesthesia was induced with thiopentone 5 mg kg^{-1} and maintained with 60% nitrous oxide in oxygen, supplemented with fentanyl 4–5 μg kg^{-1} and halothane via a face mask. The trachea was sprayed with 4% lignocaine 4 ml and was intubated without the use of neuromuscular blockers. After tracheal intubation, the end-tidal concentration of halothane was adjusted to 0.8% (1 MAC excluding nitrous oxide). The concentrations of halothane, nitrous oxide, oxygen and carbon

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TABLE I. *Patient data for 130 patients undergoing elective surgery (mean (range or* SD*) or number)*

	Pipecuronium	Vecuronium	Combination
Age (yr)	31.2 (17–53)	34.2 (18–54)	31.1 (18–47)
Weight (kg)	68.1 (12.6)	69.2 (10.7)	66 (12)
Gender (M/F)	20/20	20/20	25/25

dioxide were measured continuously by a multiple-gas analyser (Capnomac, Datex Instrumentarium, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide pressure) ($P\text{E}'_{\text{CO}_2}$ 4.7–5.3 kPa).

The ulnar nerve was stimulated at the wrist with square-wave supramaximal stimuli of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 10 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer International, Odense, Denmark). Preload tension of the thumb was maintained at 300 g throughout the investigation. The first twitch (T1) of the TOF was considered the twitch height.

When the end-tidal anaesthetic concentration had been stable for 30 min, patients were allocated randomly to receive pipecuronium, vecuronium or a pipecuronium–vecuronium combination. The following predetermined doses of drugs were administered to subgroups of 10 patients: pipecuronium 10, 20, 30 and 40 μg kg^{-1}; vecuronium 10, 20, 30 and 40 μg kg^{-1}; pipecuronium and vecuronium, respectively, 7 and 4 μg kg^{-1}, 7 and 6 μg kg^{-1}, 7 and 8 μg kg^{-1}, 7 and 10 μg kg^{-1}, 7 and 15 μg kg^{-1}. Patients were allocated at random to the subgroups and stratified sampling was used to obtain an even sex distribution. Studies of the single-drug groups were concluded first, so that doses of the combination could be planned.

All drugs were injected in 5 s into a rapidly flowing i.v. infusion. In the combination group, drugs were injected simultaneously into two separate i.v. cannulae inserted in one arm. The neuromuscular response was recorded as the maximum depression of T1, expressed as a percentage of the control value. When the maximum effect of the selected dose was reached (that is, when no further decrease in evoked response to three consecutive stimuli occurred), the study was terminated and anaesthesia continued as appropriate for surgery.

Data processing and isobolographic analysis

The percentage values for T1 depression in each group were transformed to probits and plotted against the logarithm of the dose using PCNONLIN [9]. Regression lines were compared using analysis of covariance. First, we tested the lines to determine if they deviated from parallelism; if they did not, an F test was applied to determine if the elevations were different. If so, a t test was applied to determine which line differed in elevation [10], using BMDP statistical package (1990). The ED_{50} and ED_{95} values (doses causing 50% and 95% depression of twitch tension, respectively) were calculated from the log-probit regression lines for each group. Using analysis of variance, we compared age and body weight between the groups. For all statistical comparisons, differences were considered significant when $P < 0.05$.

Isobolographic [11] and algebraic (fractional) [12] analyses were used (ED_{50} values) to define the type of interaction between pipecuronium and vecuronium. Isobolographic analysis for drug–drug interaction was conducted according to the procedure of Tallarida, Porreca and Cowan [11]. This analysis has the advantage of being independent of the slopes of the dose–response curves—that is, parallelism does not have to be established. The isobolograms were constructed by plotting single-drug ED_{50} points on the dose co-ordinates of the isobologram, and a combined ED_{50} point in the dose field. A straight line joining the single-drug ED_{50} points is termed the "additive line". If the ED_{50} of a combination falls on the theoretical additive line, the effect of the drug mixture is additive. Points to the left of the theoretical additive line would be consistent with a supra-additive, multiplicative or synergistic interaction, whereas points to the right of the line would indicate a subadditive or antagonistic interaction. Confidence intervals (CI) for each point were calculated from the variances of each component alone. CI were evaluated for statistical significance using a Student's t test.

The algebraic analysis was based on the expression of the component doses of the two agents of the combination as fractions of the doses that produce the same effect when given separately. The sum of the fractional doses, as expressed by the following equation, indicates the type of interaction:

$$dp/Dp + dv/Dv$$

where Dp and Dv are, respectively, the ED_{50} values of pipecuronium and vecuronium given alone and dp and dv are, respectively, the doses of pipecuronium and vecuronium which, when combined, are equipotent with Dp or Dv. Values near 1 indicate additive interaction, values greater than 1 imply an antagonistic interaction and values less than 1 indicate a synergistic interaction.

RESULTS

There was no significant difference between the three groups in age or weight (table I).

The dose–response curves for the first twitch height (T1) response are displayed in figure 1. Tests for parallelism revealed that these curves have different slopes ($P = 0.023$). The slope for the

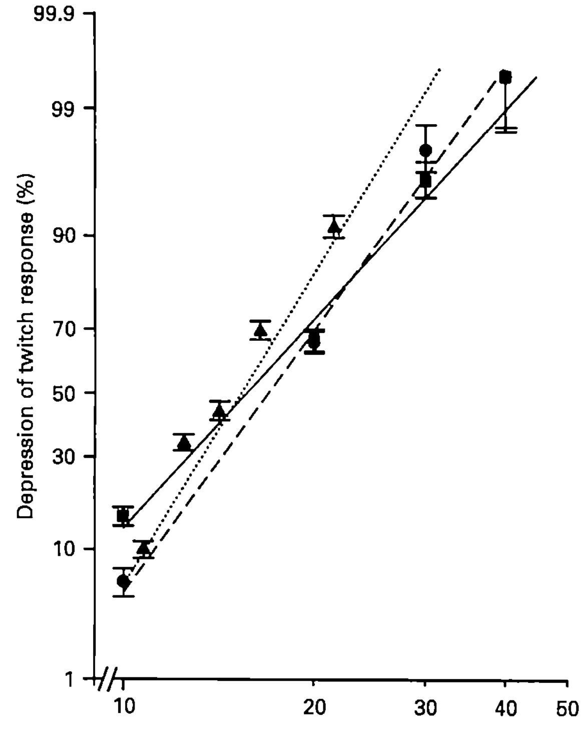

FIG. 1. Log dose-response curves for pipecuronium (●), vecuronium (■) and their combination (▲) (mean, SEM).

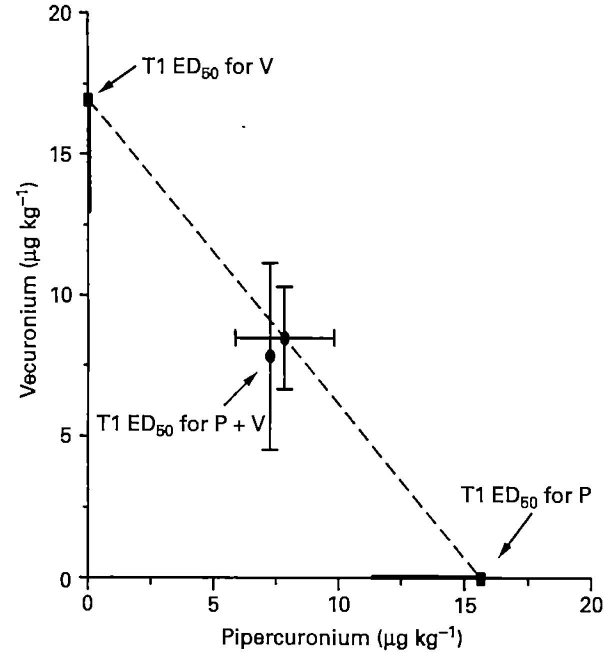

FIG. 2. T1 ED_{50} isobologram for the interaction of pipecuronium and vecuronium. The dashed line connecting the single-drug ED_{50} points is the theoretical additive line and the point on this line is the theoretical additive ED_{50} point (with SEM). The experimentally determined ED_{50} dose (with SEM) of the pipecuronium-vecuronium combination could not be distinguished from simple additive action.

pipecuronium–vecuronium combination group was numerically smaller than that for the pipecuronium or the vecuronium group: 4.2149, 5.9592 and 7.0193, respectively. Calculated ED_{50} and ED_{95} values are presented in table II.

The isobolographic analysis demonstrated an additive interaction with respect to the neuromuscular blocking activity of the pipecuronium and vecuronium combination. Figure 2 represents the T1 ED_{50} isobologram for the pipecuronium–vecuronium interaction. The experimentally determined T1 ED_{50} (CI) for the combination was 7.0 μg kg⁻¹ for pipecuronium and 7.8 (1.6–14) μg kg⁻¹ for vecuronium. The theoretical additive T1 ED_{50} (CI) was calculated to be 7.5 (4.2–10.8) μg kg⁻¹ for pipecuronium and 8.5 (5–12) μg kg⁻¹ for vecuronium. The CI of these points do overlap, and the results of a Student's *t* test for potency ratio were not significant. The fractional (algebraic) analysis of this interaction also demonstrated additivism (table III).

DISCUSSION

Isobolographic and algebraic analyses used in this study demonstrated that a pipecuronium–vecuronium combination exerted no greater effect than that seen with each agent administered alone. It has been suggested that potentiation of effect is unlikely to occur between pairs of chemically related compounds [3]. In this respect, our results are consistent with those of other investigators [13] who

TABLE II. *Calculated mean (95% confidence limits) dose–response values for depression of twitch height (T1)*

	Depression of T1 (% of control)		
	Pipecuronium	Vecuronium	Combination
ED_{50} (μg kg⁻¹)	15.6 (15.1–16.1)	16.9 (16.5–17.3)	15.0 (14.9–15.2)
ED_{95} (μg kg⁻¹)	30.6 (29.3–31.9)	28.9 (27.8–30)	23.3 (22.4–24.2)

TABLE III. *Pipecuronium–vecuronium interaction: equi-effective doses (ED_{50}) of the pipecuronium–vecuronium combination*

	Pipecuronium component		Vecuronium component		
Group	Fraction of ED_{50}	Dose (μg kg⁻¹)	Fraction of ED_{50}	Dose (μg kg⁻¹)	Sum of fractions
Pipecuronium	1	15.6	—	—	1
Vecuronium	—	—	1	16.9	1
Combination	0.45	7.0	0.46	7.8	0.91

reported an additive interaction between vecuronium and pancuronium combination in patients. On the other hand, a synergistic interaction has been demonstrated after administration of chemically related agents such as pipecuronium and vecuronium, rocuronium and vecuronium, pancuronium or pipecuronium in an *in vitro* phrenic nerve–hemidiaphragm preparation [14]. However, in the same study the authors did not observe potentiation in the effect of pancuronium–vecuronium or pancuronium–pipecuronium combinations [14]. In the above model, cumulative dose–response curves were constructed using indirectly stimulated muscle twitches to quantify relaxation [14]. Waud and Waud [6], however, gave an account of many variables that can result in inaccuracies in the *in vitro* models. Therefore, the difference observed between these experiments and the present results could be attributable to the difference in the experimental conditions (*in vitro* animal compared with *in vivo* human).

The algebraic and the geometric (isoboles) methods are used commonly for determining the nature of drug interactions. Although both methods seem closely related, it is relatively simple to interpret isobolograms. However, a known disadvantage of the isobolographic analysis is that it is readily used only with combinations of two agents, but its application to combinations of three agents is cumbersome; for the graph is in three dimensions, and it is not applicable to combinations of four or more agents. The algebraic method has no such limitations [12].

The clinical implication of our finding is that supplementation with vecuronium of an already existing pipecuronium-induced neuromuscular block is unlikely to result in potentiation of the neuromuscular block. The situation may arise in which alternate administration of neuromuscular blockers with different durations of action is undertaken if inadequate relaxation occurs near the end of the surgical procedure. This regimen has been evaluated quantitatively by Rashkovsky, Agoston and Ket [15], who have shown that, if at the time of 25 % recovery from complete pancuronium neuromuscular block 95 % paralysis is re-established with incremental doses of vecuronium, the required dose of vecuronium and the duration of paralysis are dependent on the properties of the myoneural blocker that was used initially [15].

In this study, the calculated T1 ED_{50} value for pipecuronium during 1 MAC halothane anaesthesia was 15.6 $\mu g\,kg^{-1}$. Similar ED_{50} values were reported by Wierda, Richardson and Agoston [16] (22.7 $\mu g\,kg^{-1}$) who used a single-twitch mode of stimulation and mechanomyography and by Naguib, Seraj and Abdulrazik [17] (21.2 $\mu g\,kg^{-1}$) who used an acceleration-responsive transducer under identical experimental conditions.

The ED_{50} value of 16.9 $\mu g\,kg^{-1}$ for vecuronium calculated in the present study is in close agreement with that (16.9 $\mu g\,kg^{-1}$) reported by Rupp, Miller and Gencarelli [18] during 1.2 MAC halothane anaesthesia which included a 0.6 MAC contribution from 60 % nitrous oxide. Similarly, Fisher and colleagues [19], who used single-twitch mode of stimulation and mechanomyography, reported an ED_{50} value of 15 $\mu g\,kg^{-1}$ for vecuronium during halothane (0.4–1.0 % end-tidal) and 60 % nitrous oxide anaesthesia.

There is now abundant evidence that the nicotinic acetylcholine postsynaptic receptor is a membrane-bound allosteric pentameric protein ($\alpha_2\beta\varepsilon\delta$) which alters the ion permeability of the membrane as a consequence of binding acetylcholine [20]. The term allosteric refers to a class of proteins with the characteristic that each protein is composed of subunits, contains multiple stereospecific sites for one or more ligands, and mediates indirect interactions between the separate sites. The binding sites for acetylcholine and for some pharmacological ligands, such as neuromuscular blocking agents, are located in the α-subunits [20].

Several reports have attributed the multiplicative (synergistic) effects at the neuromuscular junction which occur when two neuromuscular blocking agents are administered simultaneously to the differential pre- and post-junctional activity of different agents [2–4, 8]. The pre-junctional action consists of block of a population of nicotinic autoreceptors that are normally activated by the transmitter (acetylcholine) and that serve to mediate mobilization of reserve transmitter to the readily releasable form within the terminal axoplasm [21]. As the two binding sites for acetylcholine on the α-subunit appear intrinsically different in their binding affinities, probably as a result from the contribution of the neighbouring subunits [20], Waud and Waud [7] have suggested that potentiation can be entirely of postsynaptic origin. It is possible that the action of the drugs upon receptors on a common membrane reflects facilitation at the level of the second messenger. Considerable evidence has accumulated concerning the rule of diffusible small molecules in excitation–contraction coupling [22]. Further, the possibility that the antagonist site may be distinct from, but tightly coupled allosterically to, the agonist site has not been eliminated [23]. In addition, studies examining the synergistic interaction have not considered the possibility that the magnitude of the synergy may depend upon the intrinsic activity of different neuromuscular blocking agents.

We conclude that, in our study, the interaction of pipecuronium and vecuronium combination was the result of simple additive action at the neuromuscular junction.

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REVIEW ARTICLES

PROBLEMS ASSOCIATED WITH TRACHEAL EXTUBATION

M. HARTLEY AND R. S. VAUGHAN

All anaesthetists will, at some stage, have experienced problems after tracheal extubation. Indeed, the frequency of such problems probably exceeds those relating to tracheal intubation. Whereas a large volume of the anaesthetic literature addresses problems associated with tracheal intubation, it is unusual to find discussion concerning those following extubation. This review attempts to redress this imbalance.

DIFFICULT EXTUBATION

Difficulty in removing a tracheal tube at the end of a procedure is a rare, but dangerous and occasionally fatal complication of tracheal intubation. Blanc and Tremblay, in a review of the complications of tracheal intubation, reported that difficult extubation could be attributed to one of three basic mechanisms [7]: failure to deflate the tracheal tube cuff; an excessively large cuff catching on the vocal cords; adhesion of the tube to the tracheal wall because of an absence of lubricant. In addition, the tube may be transfixed by a suture or a wire to an adjacent structure.

In the majority of cases, however, the cause is the failure to deflate the cuff. This may occur inadvertently when a patient awakens suddenly and makes vigorous attempts to remove the tracheal tube. On other occasions, the cause is a failure of the cuff deflating mechanism, for example, when the cuff inflating tube has been clipped by artery forceps [39]. The walls subsequently remain crimped together and the cuff remains inflated, making extubation difficult. A similar outcome has been reported after the inflating port of a plastic tube was kinked by the retaining bandage attached to the tracheal tube [76].

Tavakoli and Corssen have reported an incident in which the inflating port became separated inadvertently at the point of insertion through the tracheal tube [78]. The cuff remained inflated and extubation was not possible. Direct laryngoscopy was performed and the tracheal tube withdrawn until the cuff rested against the vocal cords. It was then possible, under direct vision, to deflate the cuff by inserting a plastic cannula. The tracheal tube was removed atraumatically. These authors also suggested that, if attempts to remove a tube with a persistently inflated cuff fail, deflation of the cuff could be achieved by puncturing the cuff with a needle passed through the cricothyroid membrane when the cuff is at this level.

Brock-Utne and colleagues have recently reported an attempt to deflate the tracheal tube cuff rapidly, whereupon the pilot balloon and valve assembly were detached from the pilot tube [8]. The pilot tube was stretched, occluding the stump of the tube which was still attached to the inflated cuff, so that the tracheal tube could not be removed. Deflation of the cuff was accomplished eventually using a syringe and needle inserted into the stump of the pilot tube. These authors discourage the increasingly common practice of pulling off the pilot balloon and valve assembly in order to deflate the tracheal cuff, not only to avoid this complication, but also because it is important to have available a functional tube of the correct size, if reintubation suddenly becomes necessary.

Difficult tracheal extubation may follow forceful intubation with an inappropriately large tracheal tube [77], or may follow uneventful intubation with an appropriately sized tracheal tube in patients with a laryngeal abnormality [73]. In such circumstances, it is recommended that rotation of the tracheal tube [77] or manipulation of the larynx and tracheal tube under direct vision [73] may allow successful extubation.

Several instances of difficult extubation have been recorded as a result of sleeve formation by the cuffs of red rubber [36, 46, 49] and plastic [58] tracheal tubes. The sleeve is formed after the tracheal tube cuff is deflated and folds on itself during attempted extubation. The increase in the external diameter becomes too great for easy passage through the vocal cords. Should this occur, it is recommended that reinsertion, rotation and traction on the tracheal tube may allow successful extubation. If not, reinsertion and inflation of the cuff may smooth out the fold in the cuff and allow extubation after further deflation [49]. Other techniques using skin hooks [36] or forceps [46] to reduce the cuff fold have also been described.

The majority of reports of difficult extubation after fixation of the tracheal tube to adjacent structures have occurred in association with orofacial surgery. Surgical perforation and fixation of a nasotracheal tube has been described with both surgical wires [4, 52] and surgical screws [50]. It has

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KEY WORDS

Complications: tracheal extubation. Intubation tracheal: extubation.

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been recommended that, whenever the possibility exists of fixation of the tube during surgery, the tube should be moved up and down slightly to ensure that it has not been accidentally fixed [52]. Others have suggested the routine passage of a suction catheter down the tracheal tube when blindly directed wires or screws have been used [4]. More recently, the use of the flexible fibreoptic bronchoscope has been recommended to verify the integrity of the tracheal tube [50]; nevertheless, a patient has been reported from whom the nasotracheal tube could not be removed, despite these recommendations and manoeuvres [41]. The tube was removed subsequently without difficulty after the cuff inflating port was cut. After extubation, it was discovered that a Kirschner wire had passed between the nasotracheal tube and the cuff inflating port, thus preventing extubation. A similar incident has been recorded in which a nasogastric tube became entangled with the same port in the nasopharynx [28]. Extubation was prevented by tightening of a loop which wedged the inflating tube adaptor between the walls of the nose and the nasotracheal tube, and became possible only after the inflating port was cut just behind the adaptor.

Another case report described a nasotracheal tube being partially severed during a maxillary osteotomy procedure [71]. The partially cut tube formed a "barb" that caught on the posterior aspect of the hard palate when extubation was attempted. Tracheal extubation was possible only after the removal of the surgical sutures and wires.

Endobronchial tubes may also be fixed by the surgical procedure during thoracic surgery. Dryden reported a case of fatal circulatory collapse after the removal of a Carlens double-lumen tube which had been accidentally sutured to the pulmonary artery [23] and recommended that when endobronchial extubation proved to be difficult, fibreoptic bronchoscopy should be performed to inspect the tube for a tethering suture. A similar case presented as an impossible extubation of a left-sided double-lumen tube [1]. Fibreoptic bronchoscopy revealed adequate cuff deflation and no apparent cause of tube fixation, although the presence of blood in the left lumen was noted. A more vigorous attempt at extubation resulted in fresh bleeding from the left lumen and surgical fixation of the tube was strongly suspected. The surgical wound was reopened and removal of some sutures freed the tube. Subsequent endobronchial extubation was uneventful.

CARDIOVASCULAR RESPONSE TO EXTUBATION

Tracheal extubation is performed usually with the patient in a light stage of anaesthesia and produces significant increases in heart rate and arterial pressure which persist into the recovery period [5, 6, 25]. In 10 ASA I and II patients who were not receiving cardiovascular or antihypertensive medication, in whom extubation was performed when they were able to breathe spontaneously and open their eyes to command, Dyson and colleagues demonstrated increases of 20% or more in both heart rate and systolic arterial pressure in 70% of the patients [24].

The exact mechanism of these cardiovascular responses in man is unknown, but it is believed to be associated with the release of catecholamines causing increases in heart rate, myocardial contractility and systemic vascular resistance [66]. Recently, Lowrie and colleagues demonstrated a significant increase in the plasma concentration of adrenaline, but not noradrenaline, after tracheal extubation in a small group of patients who had undergone major elective surgery [56].

Wohlner and colleagues studied the haemodynamic responses to tracheal extubation in patients after coronary artery surgery and a period of 18–24 h mechanical ventilation [89]. They demonstrated significant increases in heart rate, mean arterial pressure, cardiac index and systemic vascular resistance index, beginning at 1 min and continuing until 10 min after extubation. They also demonstrated similar significant increases in mean pulmonary artery pressure, pulmonary artery occlusion pressure and pulmonary vascular resistance index. Other studies in similar groups of patients failed to demonstrate significant changes in some or all of these variables [26, 63]. However, the residual actions of preoperative cardiovascular medication and anaesthetic or analgesic agents may have attenuated the ability of the cardiovascular system to respond to reflex stimulation in these patients.

Clinical significance

The majority of patients are able to tolerate the haemodynamic response to tracheal extubation without any significant consequences. However, patients with co-existing disease may be unable to tolerate this response, whilst others will demonstrate an exaggerated response which itself is poorly tolerated.

In patients with coronary artery disease, the haemodynamic response to extubation may upset the balance between myocardial oxygen supply and demand, resulting in myocardial ischaemia. An ischaemic myocardial metabolic response to tracheal extubation has also been demonstrated in some patients after coronary artery surgery [26, 88]. Slogoff and Keats have shown that perioperative myocardial ischaemia is related significantly to episodes of tachycardia, but not to episodes of hypertension [72]. They have also established that the occurrence of perioperative myocardial ischaemia is associated with subsequent development of postoperative myocardial infarction and postulated a causal relationship. However, it has been suggested that a more likely explanation of the association between perioperative ischaemia and infarction is that these are two unrelated manifestations of severe underlying coronary artery disease [80]. Nevertheless, although suppression of the haemodynamic response to extubation is unlikely to influence the outcome in the majority of patients with stable coronary artery disease, there remains a small number of patients in whom a single hyperdynamic episode may produce a clinical catastrophe. Thus it seems reasonable to attempt to minimize the haemodynamic response to tracheal extubation in all patients with coronary artery disease.

In both treated and untreated hypertensive patients, emergence from anaesthesia followed by tracheal extubation is associated with significant increases in heart rate and arterial pressure. These increases mimic in size those associated with laryngoscopy and tracheal intubation in the same groups of patients [74]. It is also established that laryngoscopy and tracheal intubation in patients with hypertension, whether treated or not, produces greater increases in arterial pressure than occur in normotensive patients [66]. Thus it is reasonable to expect that hypertensive patients may exhibit an exaggerated hypertensive response to awakening and tracheal extubation compared with that seen in normotensive patients. Such hypertensive crises may result in cardiac decompensation, pulmonary oedema or cerebral haemorrhage.

The evidence of Hodgkinson and colleagues [42] suggests that, in parturients with severe pre-eclampsia, the cardiovascular response to tracheal extubation is as dramatic as the response to tracheal intubation. They demonstrated mean maximal increases of 45 mm Hg in mean systemic arterial pressure, 20 mm Hg in mean pulmonary arterial pressure and 20 mm Hg in pulmonary arterial occlusion pressure. These variables remained at values greater than the pre-extubation baseline for at least 10 min after extubation. They also reported pulmonary oedema with tracheal extubation in three patients with severe pre-eclampsia. In the *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–87* [21], hypertensive disorders of pregnancy were responsible for the second largest number of deaths (27 deaths). In the majority of these, the immediate cause of death was either pulmonary oedema (10 deaths) or cerebral haemorrhage (11 deaths). As these occurrences are likely to relate to episodes of severe hypertension, it is important to be aware of the potential of these and other patients with hypertensive disorders to show an exaggerated haemodynamic response to tracheal extubation and to attempt to minimize this response by pharmacological means.

In patients who have undergone neurosurgical operations, the postoperative period is frequently complicated by hypertension. A recent study has demonstrated that, after intracranial surgery, 91% of patients became hypertensive in the period beginning when the volatile anaesthetic was discontinued and ending after the trachea was extubated [59]. In such patients, autoregulation of cerebral blood flow may be disturbed and a sudden increase in arterial pressure may lead to increases in both cerebral blood flow and intracranial pressure. These increases may result in either herniation of brain contents or decrease in cerebral perfusion pressure, leading to cerebral ischaemia. It seems reasonable, therefore, to attempt to prevent or suppress the haemodynamic response to extubation in such patients.

Prevention

Extubation of the trachea with the patient in a deep plane of anaesthesia, achieved by inhalation or i.v. anaesthetic agents, opioid analgesics, or both, avoids cardiovascular stimulation. However, such actions may produce depression of the respiratory and cardiovascular systems and may, occasionally, result in difficulty in the management of the upper airway. A difficult mask airway, previous difficult tracheal intubation or the risk of aspiration of gastric contents therefore contraindicates such an approach.

Lignocaine has been used to suppress the cardiovascular response to extubation in patients in a light stage of anaesthesia. Bidwai, Stanley and Bidwai demonstrated that the tracheal administration of lignocaine 60 mg 3–5 min before extubation and lignocaine 40 mg at extubation prevented increases in heart rate and arterial pressure during and after tracheal extubation [6]. They subsequently demonstrated that i.v. administration of lignocaine 1 mg kg^{-1} 2 min before tracheal extubation also prevented increases in heart rate and arterial pressure during and after extubation [5]. Wallin and colleagues observed that an i.v. infusion of lignocaine 2 mg min^{-1} throughout the perioperative period suppressed extubation-induced tachycardia and hypertension [85]. However, evidence from other studies has not always supported the ability of lignocaine to suppress the haemodynamic response to tracheal extubation, by either route of administration [25, 89].

Recently, the effects of pharmacological agents acting directly on the cardiovascular system have been investigated. The cardioselective beta-adrenoceptor antagonist, esmolol, given in a dose of 1.5 mg kg^{-1} i.v. 2–5 min before tracheal extubation, has been shown to attenuate the increases in heart rate and arterial pressure that occur in healthy patients at extubation without producing the decreases in heart rate and arterial pressure which may occur with larger doses [24]. The rapid onset and short duration of action ($T\frac{1}{2} = 9$ min) of esmolol make it an ideal agent to prevent acute increases in heart rate and arterial pressure which occur at extubation [35].

In neurosurgical patients, the use of agents that relax vascular smooth muscle to control the increase in arterial pressure at extubation should be avoided, as the resultant cerebral vasodilatation may increase cerebral blood volume and thus intracranial pressure.

The use of alpha- and beta-adrenergic receptor antagonists has been advocated in such patients [83]. The combined alpha- and beta-adrenoceptor antagonist, labetalol, has been compared with esmolol to treat patients after craniotomy who exhibited significant hypertension after tracheal extubation [59]. Both esmolol and labetalol were effective in treating hypertension, but decreases in heart rate were more frequent in the immediate postoperative period in patients given labetalol.

COMPLICATIONS AFTER TRACHEAL EXTUBATION

Trauma

Trauma to any of the structures forming the upper and lower airways is possible at tracheal extubation, but it has rarely been reported. Trauma to the larynx and vocal cords is particularly likely after a difficult extubation and it has been recommended that direct laryngoscopy should always be performed immediately after extubation to assess any laryngeal damage if attempts to remove a tracheal tube have been forceful and repeated [49]. In addition, damage to the mobile structures in the upper airway as a result of excessive suction at the time of extubation should always be considered.

The sequelae of trauma to the laryngeal structures may only become apparent at or soon after extubation, although the trauma may have occurred at an earlier stage of the intubation process. Dislocation of the arytenoid cartilages has been described after a difficult intubation [81], but has also followed uncomplicated tracheal intubation [31]. The usual presentation is painful swallowing and voice change, but the condition may also present as acute respiratory failure because of upper airway obstruction immediately after extubation [11, 14, 81]. This injury should be considered in all patients who experience signs of upper airway obstruction in the early period after extubation. It has been suggested also that arytenoid dislocation may have been the cause of some of the cases described previously as "glottic oedema" occurring after tracheal extubation [11]. Management requires immediate reintubation and the subsequent treatment involves either early reduction of the arytenoids by application of gentle pressure with a laryngeal spatula or prolonged tracheal intubation, or even tracheotomy, to prevent arytenoid movement and enable healing of the dislocated joint [11].

A recent case report described a lung laceration, with subsequent pneumothorax and lung abscess, after tracheal extubation over a tracheal tube changer during which the changer was advanced until a firm resistance was felt [55], yet it has been suggested that a gum elastic bougie be left in the trachea after tracheal extubation of patients with abnormal airway anatomy to assist if emergency reintubation is required [82]. The recommended technique for ascertaining tracheobronchial placement of the bougie is the detection of resistance to further passage of the stylet [47]. The authors of this case report disagreed with this recommendation and suggested that measurement and use of markings to limit the depth of insertion are warranted.

Tracheal collapse

Tracheomalacia may be primary or secondary (usually to thyroid pathology), but may produce upper airway obstruction only after tracheal extubation. Blanc and Tremblay described a case of tracheomalacia in a 14-yr-old boy, secondary to Pott's disease of the cervical spine [7]. Respiratory obstruction occurred after retraction of the tracheal tube 4–5 cm from the carina and was corrected only by reinserting the tube to within 1–2 cm of the carina. They recommended that, in such patients, tracheal extubation should be performed slowly. If ventilatory obstruction should occur, the tracheal tube should be repositioned and retained until surgical correction of the lesion is possible.

Tracheomalacia may result from prolonged compression by an expanding thyroid goitre, particularly within the confines of the thoracic inlet. The cartilaginous rings supporting the trachea may be weakened or even destroyed, compromising the structural integrity of the upper airway after the extrinsic compression is relieved. Tracheal collapse usually occurs after extubation and requires emergency reintubation. The subsequent options include surgical resection of the affected segment of the trachea, internal or external tracheal support, or airway diversion below the affected trachea through a tracheostomy. These options have recently been reviewed by Geelhoed [32].

Airway obstruction

Laryngospasm, laryngeal oedema and vocal cord paralysis are important causes of upper airway obstruction occurring immediately after extubation. They will be discussed separately. It is also important to remember causes of airway obstruction relating to foreign bodies such as throat packs, dentures and blood clots. All require immediate removal to relieve the obstruction.

In some subjects, airway obstruction occurs as a consequence of the surgical procedure—for example, haemorrhage complicating thyroid surgery [84] or other procedures in and around the neck [9, 18]. It has been suggested that the upper airway obstruction in such patients may result from laryngeal and pharyngeal oedema secondary to venous and lymphatic congestion, rather than compression of the trachea by haematoma [38]. In the case of post-thyroidectomy bleeding, immediate release of the wound sutures may produce dramatic improvement, although definitive treatment requires tracheal intubation followed by surgical decompression and control of the source of bleeding.

Laryngospasm

Laryngospasm has been defined as an occlusion of the glottis by the action of the intrinsic laryngeal muscles [68]. The structural and functional basis of the laryngospasm reflex has been reviewed in detail by Rex [68]; it is essentially a protective reflex, mediated by the vagus nerves, which acts to prevent foreign material entering the tracheobronchial tree.

Laryngospasm is the most common cause of upper airway obstruction after tracheal extubation. It is particularly frequent in children after upper airway surgery, for example after adenotonsillectomy, with which the incidence is approximately 20 % [2, 54]. It is precipitated by local irritation of the vocal cords by secretions or blood, when the plane of anaesthesia is insufficient to prevent the laryngospasm reflex, but too deep to allow co-ordinated cough. Thus it is most likely to occur after tracheal extubation of a patient in a plane of anaesthesia somewhere between an awake and a deeply anaesthetized state.

The evidence relating frequency of laryngospasm and other airway-related complications, including arterial oxygen desaturation, to tracheal extubation performed in awake compared with deeply anaesthetized patients is conflicting. Patel and colleagues did not demonstrate any significant difference in the incidence of such complications between tracheal extubations undertaken in subjects awake or anaesthetized after either adenotonsillectomy or strabismus surgery, in children who had been anaesthetized with nitrous oxide and halothane [62]. In contrast, the study of Pounder, Blackstock and Steward suggested that, in children undergoing minor surgery not involving the airway, awake extubation after either halothane or isoflurane anaesthesia was associated with a greater likelihood of arterial oxygen desaturation than occurred with tracheal extubation of deeply anaesthetized subjects [65]. In addition, while there was no significant difference in the incidence of airway-related complications between the two agents if the trachea was extubated while the children were deeply anaesthetized, isoflurane was associated with more airway-related complications than halothane in children undergoing tracheal extubation whilst awake. This study must not be interpreted to imply that the trachea should always be extubated while children are deeply anaesthetized. There are many patients, such as those with a full stomach or those whose airway is difficult to manage, who should be awake and able to maintain and protect the airway immediately after extubation.

Lignocaine has been used to prevent extubation laryngospasm after tonsillectomy. Baraka studied 40 children after tonsillectomy and showed that none of the 20 children who had received an i.v. injection of lignocaine 2 mg kg^{-1} 1 min before extubation developed laryngospasm after tracheal extubation. In the control group, four of 20 children developed severe laryngospasm after extubation of the trachea [2]. In a similar study in adults after tonsillectomy, no patient in either the lignocaine or the control group developed laryngospasm. However, lignocaine 2 mg kg^{-1} i.v. 2 min before removal of the tracheal tube did significantly reduce the incidence of coughing after extubation [33].

Leicht, Wisborg and Chraemmer-Jorgensen questioned this prophylactic effect of lignocaine [54]. They studied 100 children after tonsillectomy in whom lignocaine 1.5 mg kg^{-1} was administered i.v. before tracheal extubation, which took place at a consistent depth of anaesthesia, namely when there were signs of swallowing. There was no difference in the incidence or severity of laryngospasm between this group and a control group using these dosages and timing schedules. The results of this study suggest that the beneficial effects of lignocaine demonstrated by Baraka may have been attributable to a central increase in the depth of anaesthesia. Therefore, to derive maximum benefit from the central nervous system depression produced by lignocaine, tracheal extubation must be performed before signs of swallowing activity occur.

Laryngospasm presents as a spectrum ranging from mild inspiratory stridor to complete upper airway obstruction. Although the former is not life-threatening, it may progress rapidly to the latter if managed incorrectly. Complete upper airway obstruction results in the loss of inspiratory stridor and it is of paramount importance that this "silence" is not mistaken for an improvement in the clinical state.

Management of laryngospasm after tracheal extubation may follow one of two lines of treatment. After any precipitating cause has been identified and removed by direct laryngoscopy and suctioning of the laryngo-pharynx:

(1) 100% oxygen must always be administered, if necessary by positive pressure ventilation until, as the patient awakens, laryngospasm disappears.

(2) The plane of anaesthesia may be deepened using i.v. or inhalation anaesthetic agents until laryngospasm and other reflexes are abolished.

However, as these methods are not always successful, it is sometimes necessary to administer the short acting neuromuscular blocking agent, suxamethonium chloride, to enable oxygenation of the patient and, if required, tracheal intubation [17]. Some anaesthetists also give i.v. atropine before suxamethonium, particularly for repeated doses or if there is hypoxia. The threshold to establish muscle paralysis and ventilation should be determined by the arterial oxyhaemoglobin saturation as indicated by pulse oximetry. Thus, faced with a patient who develops laryngospasm after tracheal extubation and an arterial oxyhaemoglobin saturation that decreases to less than 85%, it is reasonable to suggest these further measures.

Older textbooks of anaesthesia recommended the use of atropine or other anticholinergic agents as a treatment for laryngospasm. In a review of this practice, Rosen argued that atropine is of no value as either prophylaxis or treatment of reflex laryngospasm [69]. However, anticholinergic agents may be useful to remove some of the predisposing causes of laryngospasm by suppressing the secretion of saliva and mucus which may stimulate laryngospasm should they enter the upper respiratory tract.

Other measures have been recommended to treat laryngospasm after extubation. Baraka administered lignocaine 2 mg kg^{-1} i.v. to the four children in his control group who developed severe laryngospasm following extubation; this was successful in these children within 30–90 s [2]. Owen reported the successful use of an i.v. injection of doxapram 1.5 mg kg^{-1} in five patients who had developed laryngospasm after extubation and noted that cessation of laryngospasm was immediate in all patients [61].

Laryngeal oedema

Laryngeal oedema is an important cause of upper airway obstruction after tracheal extubation in children and, more particularly, in neonates and infants. The oedema may be localized to the supraglottic, retroarytenoidal or subglottic regions [7].

Supraglottic oedema. Oedema occurs in the loose connective tissue on the anterior surface of the epiglottis and on the aryepiglottic folds. The epiglottis may be displaced posteriorly by the swelling, blocking the glottic aperture on inspiration and resulting in severe acute upper airway obstruction.

Retroarytenoidal oedema. Oedema occurs in the loose connective tissue just below the vocal cords and behind the arytenoid cartilages. Movement of the arytenoid cartilages is thus restricted and this limits abduction of the vocal cords on inspiration.

Subglottic oedema. The subglottic region has fragile respiratory epithelium with loose submucosal connective tissue that is easily traumatized and prone to oedema. The non-expandable cricoid cartilage, which encircles the subglottic region, is the narrowest part of the airway in children and limits the outwards expansion of the oedema.

Subglottic oedema is a particular problem in neonates and infants, in whom a minor degree of oedema may produce a significant reduction in the internal laryngeal cross-sectional area. This area in the newborn is no greater than 14 mm^2, and a 1-mm thick layer of oedema in the subglottic region reduces this area to 5 mm^2 (35 % of normal) [75]. In an adult, this degree of oedema would not cause significant obstruction.

The incidence of oedema after tracheal extubation of children and the factors contributing to its development were established in a prospective study by Koka and colleagues [48]. They found an overall incidence of 1 % in children younger than 17 yr, with those younger than 4 yr particularly susceptible. Factors that showed a significant positive correlation with the development of laryngeal oedema were the use of a tight-fitting tracheal tube, occurrence of trauma at tracheal intubation, a duration of intubation greater than 1 h, coughing on the tracheal tube or a change in position of the patient's head and neck during surgery. Surprisingly, the presence of upper respiratory tract infection was not a significant contributory factor.

Laryngeal oedema presents as inspiratory stridor, usually within 6 h of extubation. In such patients, movement of respired gases must be confirmed repeatedly, as diminishing stridor may represent impending complete upper airway obstruction rather than resolving oedema.

Management of laryngeal oedema after extubation of the trachea depends upon its severity. Mild cases may respond to conservative measures, with inhalation of a humidified and warmed, oxygen-enriched gas mixture. Nebulized adrenaline 1:1000 (0.5 ml kg^{-1} up to 5 ml) has been recommended in the management of infective croup in children [67] and has also been used successfully in the management of laryngeal oedema after tracheal extubation [15, 16, 37]. Relief is dramatic, but short-lived, and additional nebulized adrenaline may be required at regular intervals.

The value of systemic steroids is less clear. I.v. dexamethasone 0.25 mg kg^{-1} immediately, followed by 0.1 mg kg^{-1} 6 hourly for 24 h has been recommended [40], although recent studies in both children and adults indicated that dexamethasone was ineffective in the prevention of laryngeal oedema after tracheal extubation [20, 29, 79].

More severe cases of oedema after extubation, or those which fail to respond to the above measures, may require a period of reintubation with a smaller tracheal tube.

Vocal cord paralysis

Vocal cord paralysis resulting from trauma to the vagus nerves or their branches is an important, although rare, cause of upper airway obstruction after extubation. The rarity of the condition was confirmed in a prospective study by Walts, Calcaterra and Cohen, who visualized the vocal cords of 100 patients after tracheal extubation, none of whom showed any evidence of vocal cord paralysis [86].

Unilateral vocal cord paralysis is usually a benign condition which presents as hoarseness in the early postoperative period followed by recovery over several weeks. Bilateral vocal cord paralysis is a more serious condition which may present as upper airway obstruction immediately after extubation. The usual methods of relieving upper airway obstruction are not effective, although assisted ventilation with a facemask may overcome the upper airway obstruction. Laryngoscopy reveals motionless vocal cords which lie adducted with a very narrow glottic aperture. Immediate insertion of a tracheal tube eliminates the upper airway obstruction. Recovery is usual but often delayed, and a tracheostomy may be required temporarily.

Vocal cord paralysis is described usually after surgical procedures involving the head and neck, the thyroid gland or the thoracic cavity. It has also been described in association with increased intracranial pressure, when it may present as upper airway obstruction after tracheal extubation [13, 64]. Vocal cord paralysis has also occurred unexpectedly after surgery remote from the head and neck [34, 43, 60]. It has been suggested that tracheal intubation itself may result in peripheral nerve damage leading to vocal cord paralysis. Cavo has listed approximately 30 reports of true vocal cord paralysis in which tracheal intubation appeared to be the only explanation for the peripheral nerve damage [12]. He has also confirmed the cadaver study of Ellis and Pallister [27], who determined the course of the recurrent laryngeal nerves which, after leaving the thorax, travel in the oesophagotracheal groove towards the larynx where they divide into anterior and posterior branches. The anterior branches were found to be susceptible to compression by the tracheal tube cuff where they lie beneath the mucosa and immediately medial to the lamina of the thyroid cartilage.

Pulmonary oedema associated with upper airway obstruction

The development of pulmonary oedema after an episode of acute upper airway obstruction is a phenomenon which is being described more frequently. There are numerous reports, in both children and adults, of pulmonary oedema complicating upper airway obstruction after tracheal extubation [3, 19, 22, 30, 44, 45, 53, 57, 70, 87].

The clinical presentation, management and pathogenesis of pulmonary oedema associated with upper airway obstruction have been reviewed recently by Lang and colleagues [51]. The onset of the pulmonary oedema is usually within minutes of either development of acute upper airway obstruction or after relief of obstruction. Resolution usually occurs spontaneously over a period of a few hours. The essentials of management are maintenance of the airway by tracheal intubation, administration of supplementary oxygen and, if necessary, institution of positive pressure ventilation until the condition resolves. The majority of patients do not require either aggressive haemodynamic monitoring or drug therapy. The pathogenesis of the pulmonary oedema is multifactorial, although the markedly negative intrathoracic pressure generated during an episode of acute upper airway obstruction is probably the dominant pathophysiological mechanism.

Laryngeal incompetence

Aspiration of gastric contents or foreign bodies at tracheal extubation may occur in patients whose protective laryngeal reflexes are obtunded by the residual effects of local or general anaesthetic agents. In addition, the work of Burgess and colleagues suggests that laryngeal function is disturbed for at least 4 h after tracheal extubation, even in alert postoperative patients [10]. The mechanism of this laryngeal incompetence after extubation of the trachea is thought to be inability of the larynx to sense foreign material. The best protection against pulmonary aspiration is obtained by pharyngeal suction under direct vision, followed by extubation in the lateral position with head-down tilt.

NOTE ADDED IN PROOF: Since this review was accepted for publication, another treatment for laryngospasm has been recommended. I.v. diazepam has been used successfully to abolish the spasm, although the dose per kg is not stated [Gilbertson AA. Laryngeal spasm. *British Journal of Anaesthesia* 1993; 71: 168–169].

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ANAESTHESIA FOR CAROTID ARTERY SURGERY

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Transient ischaemic attack, reversible ischaemic neurological deficit and progressive or complete stroke are leading causes of morbidity and mortality in the Western World. In the United Kingdom, stroke accounts for an annual mortality of 10 deaths per 100 000 of population at age 40 yr, increasing to 1000 deaths per 100 000 at age 75 yr. Transient ischaemic attacks are estimated to affect, on average, 0.5 per 1000 of the general population at any age, becoming more common in the elderly.

Commonly, these focal ischaemic events are the result of artery-to-artery embolization of aggregates of platelets and fibrin, or of cholesterol and atheromatous debris. Stenotic arterial lesions and ulcerated atheromatous plaques, at sites of predilection for atherosclerotic lesions in the cervico–cranial arteries, are the commonest sources of such emboli.

Other causes of cerebral ischaemia include emboli from the heart and lacunar infarcts in the brain [8]. The endothelial surfaces of the heart which may be damaged include congenital bicuspid aortic valves and surgically-placed prosthetic valves. Mural thrombus, endocarditic vegetations or atrial myxoma may produce similar effects. Atrial fibrillation associated with any of the former greatly increases the frequency of cerebrovascular events. Lacunar infarcts occurring within the brain are solely attributable to atherosclerotic, hypertensive and vascular disease [32]. Stenosis of the internal carotid artery is one of the primary sources of cerebral emboli [9, 37] and removal of the atheromatous plaque without leaving loose arterial intima distally is the aim of surgical reconstruction of the artery. The end result of surgery should be a smooth arterial wall and blood-tight closure [76], thereby preventing future embolic phenomena.

THE OPERATION

The first operation for carotid occlusive disease was carried out by Eastcott, Pickering and Robb at St Mary's Hospital, London in 1954 [28]. Since then, carotid endarterectomy has become relatively frequently performed in the U.K. [56] and is one of the commonest vascular procedures in the U.S.A. where it is performed between 19 and 27 times more frequently in that country than in the U.K. [10, 70]. The differences in practice on either side of the Atlantic probably derive from differences in the referral mechanism: most British surgeons receive patients from neurologists, who are more likely to evaluate medical therapy first, whereas direct referral from a general practitioner to a vascular surgeon is commoner in the U.S.A. American surgeons are also more likely than their British counterparts to operate for asymptomatic bruit or frank stroke.

As with every operation, it is important to take all risks to the patient into account and weigh them against the advantages of a successful procedure. If the operation is to be undertaken, the ultimate goal of surgery and anaesthesia is maintenance or improvement of oxygen delivery to potentially ischaemic brain tissue. Currently, no surgical technique prevents the transient occlusion of the blood flow to the brain. During unilateral carotid occlusion, the delivery of oxygen to the compromised hemisphere can be maintained only by collateral flow via the Circle of Willis or the vertebral arteries. Minimal amounts of flow also arise from meningeal arterial branches that originate from the external carotid and the ophthalmic artery. Studies in primates suggest that unilateral carotid occlusion decreases perfusion pressure in the ipsilateral middle cerebral artery by only 14% [83]. However, this does not provide comfort for the anaesthetist during carotid endarterectomy, as the circulation under consideration is often that of an elderly atherosclerotic patient in whom collateral flow is poor.

Cerebral autoregulation is the ability of the brain to maintain constant cerebral blood flow over a wide range of perfusion pressures. With intact autoregulation, total cerebral blood flow approaches 50 ml min^{-1}/100 g of brain. Critical blood flow, less than that at which damage occurs to cerebral tissue, has been shown to be 18–24 ml min^{-1}/100 g. Over a range of mean arterial pressure of 60–180 mm Hg, flow greater than this critical value provides the oxygen necessary for adequate cerebral metabolism—3 ml min^{-1}/100 g of brain.

The surgical technique associated with carotid

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endarterectomy has improved steadily. Most surgeons make a skin incision anterior to the sternocleidomastoid muscle. The carotid artery is dissected carefully, with as little manipulation as possible, and systemic heparin is given by the anaesthetist. The vessel is then occluded above and below the lesion, with careful protection of the vagus and hypoglossal nerves. A longitudinal arteriotomy is made extending above and below the plaque, which is then dissected away from the intima or adventia.

The use of systemic heparin, a heparin-impregnated shunt, or both, provides the surgeon with adequate time for endarterectomy. The use of a shunt is controversial, as good results have been reported both with [84] and without its use [62]. Those favouring a shunt argue that it maintains blood flow to an already compromised cerebrovascular bed. The procedure does, however, add to operative time and complexity, may not be performed easily, and carries a risk of inducing embolization. The shunt may lead to further intimal damage to the vessel wall and may obstruct surgical access.

ANAESTHETIC CONSIDERATIONS

Preoperative Assessment

Patients presenting for carotid artery surgery are frequently elderly and may be expected to have coexisting medical problems common to patients with vascular disease: chronic obstructive airway disease and diabetes. An increase in systemic arterial pressure is found in up to 70% of patients presenting for carotid endarterectomy and is the major risk factor in stroke [27], even if the hypertension is minimal or only systolic in nature [42]. The pathophysiology of hypertension also leads to an impairment of cerebral autoregulation [80] and a decrease in regional cerebral blood flow [68]. Not surprisingly, it has been shown that control of hypertension in the preoperative period reduces the incidence of postoperative hypertension and neurological deficit [6].

In addition to hypertension, the presence of cardiac disease should be suspected and sought. Silent cardiac disease, complicated by transient ischaemic attacks, has an annual mortality rate of 5% which nearly equals the mortality from asymptomatic three-vessel coronary artery disease (6%) [1]. Myocardial infarction is a major complication of carotid endarterectomy and is the most frequent cause of perioperative mortality [13, 24, 40].

Other medical problems frequently complicate the management of carotid endarterectomy.

Smoking

Many patients who present for carotid endarterectomy are, or were, smokers. They may be expected to have some degree of airway obstruction and suffer from postoperative ventilatory difficulty because of reactive airways, excess secretions and lung closing volumes which exceed tidal volumes—thus leading to atelectasis and secondary ventilation/perfusion mismatch. Correct preoperative preparation of such patients is important and the physiotherapist can help by teaching breathing exercises, the use of incentive spirometry and techniques to aid expectoration of secretions. Appropriate use of bronchodilators and antibiotics and the cessation of smoking also help to improve postoperative recovery.

Diabetes

Diabetic patients have a high incidence of vascular disease. Preoperative assessment should establish the diabetic type and current medical treatment (diet alone, oral hypoglycaemic agents or insulin).

Diabetic control should be evaluated and, where necessary, stabilized—as should the complications of chronic diabetes such as peripheral neuropathy, renal insufficiency or cardiomyopathy. Diabetic patients may require the use of glucose-containing solutions for intraoperative management of blood-sugar concentration, although these solutions should be avoided in other patients, for reasons explained later.

Other factors

Preoperative evaluation should be thorough, with particular emphasis on the nature, frequency and date of onset of the patient's symptoms, if any, of carotid arterial insufficiency. A drug history and general review of systems should be undertaken. Particular attention should be devoted to the measurement of systemic arterial pressure. Values should be obtained in both arms, and with the patient supine and standing. A cardiac history and extensive cardiac evaluation should be undertaken whether or not the patient is symptomatic. ECG and chest x-ray are mandatory. An exercise ECG is of additional value.

If general anaesthesia is being considered, positioning of the patient's head is an important consideration. Many patients have cervical spondylosis, vertebro–basilar insufficiency, or both, and inappropriate operative positioning may exacerbate or cause neurological damage. Preoperative neurological examination of the patient facilitates early recognition of postoperative central nervous system dysfunction which may necessitate prompt pharmacological or surgical intervention.

In summary, adequate control of arterial pressure and an optimal general medical status should be obtained as far as possible before elective carotid surgery. In most instances, the patient's routine medication should be continued on the morning of surgery. This applies especially to beta-adrenoceptor blockers, calcium antagonists and centrally acting antihypertensive drugs, as these agents are associated with rebound hypertension if stopped abruptly.

Premedication

Good rapport should be established with the patient in the preoperative period when possible. An adequate and sensitive preoperative interview including an open, non-technical explanation of the perioperative events should help to alleviate preoperative anxiety. This is important, as anxiety in this patient population exacerbates the potential hazards of surgery such as perioperative hypertension, myocardial ischaemia, cardiac arrhythmia and potentially fatal myocardial infarction. In the opinion of the authors, light premedication with benzodiazepines is also justified to ameliorate anxiety and consequent tachycardia and hypertension. A delicate balance must be maintained, however, as oversedation may depress the neurological status of the patient leading to hypotension, hypercapnia, or both, with consequent detrimental effects on the cerebral circulation [18, 31].

Intraoperative Management

Myocardial and cerebral ischaemia must be prevented. While most cerebral morbidity is thought to be caused by emboli either resulting from the disease itself or associated with the surgical intervention, the anaesthetist can greatly influence the overall success of the procedure. Optimizing cerebral perfusion, manipulating cardiovascular physiology and monitoring the patient appropriately to allow early intervention to prevent potential neurological or cardiovascular mishaps are vital functions performed by the anaesthetist.

Adequate monitoring is of crucial importance. Continuous ECG is mandatory, with the ability to record from limb and precordial leads an advantage. An indwelling arterial catheter should be used for direct monitoring of systemic arterial pressure and collection of blood for measurement of arterial blood–gas tensions and other laboratory tests. The pulse oximeter provides not only a continuous estimate of blood oxygen saturation, but also the detection of a peripheral pulse. Temperature monitoring is a useful aid to maintenance of cardiovascular stability and also to estimation of appropriate timing of awakening and antagonism of neuromuscular block. As large blood losses or fluid loads are not usually associated with the procedure, central venous or pulmonary artery catheterization is unnecessary unless the cardiovascular system is unstable (recent myocardial infarction [66]) or there is a history of congestive heart failure or poor left ventricular function (ejection fraction less than 0.5) [49]. Several monitoring techniques to assess the adequacy of cerebral perfusion have been used during anaesthesia. However, neurological well-being can only be demonstrated fully if the entire procedure is conducted using a regional anaesthetic technique. This allows continuous monitoring of cerebral function by observation of, and verbal communication with, an awake patient.

In the unconscious patient, other less reliable methods of assessing cerebral perfusion must alert the anaesthetist and surgical team to impending neurological deficit. No single technique is perfect, but those available include the electro-encephalograph (EEG) [5], evoked potential monitoring [43], measurement of regional cerebral blood flow by intra-arterial injection of xenon-133 and subsequent scintillation counting over the brain [73], measurement of distal carotid stump pressure to assess adequacy of cross-over flow from the contralateral carotid artery [47], and those tests which may also be used in preoperative carotid evaluation, namely, oculoplethysmography [63], angiography [57, 69] and Doppler ultrasound [92].

The variable measured most commonly is the perfusion pressure as reflected by the stump, or carotid occlusion, pressure [82]. Stump pressure is that pressure measured distal to the surgically occluded carotid artery and is thought to equal the collateral perfusion pressure via the Circle of Willis. Critical stump pressure (the minimum required to avoid inadequate collateral flow) is considered to be in the range 50–60 mm Hg. At values smaller than this, most surgeons who make this measurement consider a bypass shunt necessary to maintain perfusion.

EEG changes indicative of ischaemia lasting 10 min or more have been shown to correlate with new postoperative cerebral ischaemic changes [65]. Problems with the EEG primarily involve interpretation, as most anaesthetists are not skilled in this technique. Also, by the time that an EEG trace shows an abnormality, it may no longer be possible to correct the neurological deficit by restoration of cerebral perfusion. The monitoring of somatosensory evoked potentials (SSEP) has been shown to be as sensitive and specific as the EEG in detecting cerebral ischaemia during carotid endarterectomy; a decrease in SSEP amplitude (greater than 50%) may be a better indicator of ischaemia than an increase in latency [66]. Delayed detection of neurological damage is obviously a major drawback of general anaesthesia.

Cerebral Protection

Any anaesthetic technique should attempt to protect the brain from hypoxic damage. This may be achieved under general anaesthesia by decreasing the cerebral metabolic rate for oxygen. The administration of a barbiturate is still the only proven mechanism allowing this to occur in humans by depression of metabolism in actively metabolizing brain [48]. Thiopentone has the effect of reducing intracranial pressure [46], which may be of benefit in carotid endarterectomy. Other cerebroprotective advantages of barbiturates include inhibition of oxygen free radical formation [78], reduction of cerebral oedema [77] and a more recently discovered sodium channel blocking action [34]. Barbiturates do not, however, provide protection from global ischaemia—as recent evidence from post cardiac arrest victims shows. When ischaemia is present, barbiturates do not aid resuscitation [17].

Of the other induction agents, ketamine should be avoided as it increases both flow and $CMRo_2$. Etomidate reduces $CMRo_2$ and may be cerebroprotective but, unfortunately, acts as a cerebral vasoconstrictor before suppressing $CMRo_2$ [89]; it also suppresses the adrenocortical axis. Midazolam reduces $CMRo_2$ and has demonstrated cerebroprotective qualities in animals [11]. As it has relatively mild haemodynamic effects if used correctly, it may well have a place, in conjunction with barbiturates, as a useful induction agent. Propofol still remains to be fully evaluated in this setting, but early laboratory evidence is not encouraging [90]. Recent work evaluating the effect of propofol infusions on cerebral circulation and autoregulation in anaesthetized baboons showed that a dose-dependent decrease in cerebral blood flow occurred.

This may be of advantage in carotid artery surgery; however, the effect on cerebral metabolism was more equivocal and the authors suggested that further studies are needed to evaluate the influence of propofol on the coupling between metabolism and blood flow [87]. The rapid awakening associated with propofol anaesthesia is also an attractive feature of the drug, but further information is needed before the use of propofol can be endorsed.

In addition to the above "anaesthetic" drugs, several other drugs are currently being evaluated for use as cerebroprotective agents. Nimodipine, a calcium channel blocker, has been shown to be efficacious in this regard. It has been of proven benefit in the treatment of vascular spasm after subarachnoid haemorrhage [4]. Interestingly, it is not clear if this agent acts by an effect on the vascular smooth muscle or if its primary mechanism of action is directly on the neurone. Whether prophylactic use of nimodipine is warranted in patients undergoing carotid endarterectomy has still to be investigated and it is likely that evidence will derive from neurosurgical observations.

Other drugs potentially offering pharmacological brain protection act via a variety of means and still remain experimental. Antagonists of excitatory neurotransmitters (e.g. dizocilipine maleate) are cerebroprotective in lower mammals (e.g. rats, mice), but their effect is insufficient to allow the more complex areas of primate brain, exquisitely dependent on adequate oxygenation, to be protected. Dizocilipine maleate may, however, have a place in regional incomplete ischaemia such as may occur in carotid endarterectomy, although much work remains to be done before this agent can be recommended clinically [51].

Free radical scavenging may provide a means of defence against ischaemic brain damage. Methylprednisolone has recently been suggested to improve outcome in spinal cord injury if given within 8 h of the injury [16]. Whether this drug has a place in cerebral protection has yet to be demonstrated. Proven laboratory evidence shows the free radical scavenger U74006F, a 21-amino steroid, to have marked cerebroprotective properties in dogs, but only if given before the period of ischaemia [51]. As yet, no clinical use of this product has been permitted, but it is interesting to speculate about its future place in cerebroprotection.

Non-pharmacological means of cerebroprotection worthy of discussion include hypothermia and control of blood-glucose concentration.

Hypothermia (to temperatures less than 32 °C) has found a place in the management of cardiopulmonary bypass by reducing cerebral metabolic rate and thus increasing the tolerance of the brain to ischaemia. This mechanism differs from barbiturate-induced reduction of $CMRo_2$ as the effect of decreased metabolism is global, barbiturates affecting primarily the metabolic rate of the actively working brain.

Why, therefore, is hypothermia not utilized more often for carotid surgery? Unfortunately, the integrity of neuronal membranes is not guaranteed with deep hypothermia. In fact, a hypothermic brain is similar to a hypoxic brain in that intracellular ionic leak is induced, albeit to a much lesser degree [54]. The attainment of hypothermia is also difficult without the facility of cardiopulmonary by-pass and adds significantly to the duration of anaesthesia. Thus, on balance, deep hypothermia is of little benefit. In contrast, mild hypothermia (temperature about 35 °C) may be achieved easily and may decrease cerebral metabolism sufficiently (in this particular context) with no obvious disadvantages.

Hyperglycaemia worsens ischaemic brain damage and should be avoided [64]. Laboratory evidence suggests that even mild increases in blood-sugar concentration worsen the prognosis for the ischaemic brain [44]; thus maintenance of normoglycaemia during surgery is important. The use of glucose-containing fluids during operation should be considered with this in mind. Obviously, the diabetic patient represents a class of subject in whom meticulous blood-glucose control is mandatory and the use of glucose-containing solutions may be necessary.

Choice of Technique

It is the aim of the anaesthetist to maintain normocapnia, normotension or slight hypertension, mild anticoagulation and normovolaemia by careful choice of drugs and fluids.

Regional anaesthesia

Several authors have reported low morbidity and mortality associated with the use of regional anaesthesia for carotid endarterectomy [15, 19, 22, 36, 81]. Two different methods may be used: combined deep and superficial cervical block or cervical extradural anaesthesia. Both of these techniques are unfamiliar to most anaesthetists, leading to a natural reluctance to perform either. Identification of the second, third and, occasionally, fourth cervical roots is needed to perform deep cervical block. In addition, superficial block is necessary because of communication between the trigeminal nerve and the lower cervical plexus. Unfortunately, even in experienced hands, the block is associated with a high failure rate (20 %) [12]. In addition, discomfort may still be felt by the patient because of difficulty in anaesthetizing the carotid sheath—leading to a requirement for additional infiltration during the operation.

An alternative regional technique is that of cervical extradural block. Originally performed by Dogliotti [25] in 1933 for thoracic surgery, this block has been used most frequently for chronic head or neck pain associated with Pancoast syndrome. Bonnet and colleagues [15] reported a series of 394 consecutive patients (undergoing carotid artery surgery) operated on under cervical extradural block with apparently good results. Patients in the sitting position had an 18-gauge Tuohy needle placed by the midline approach into the C6–7 or C7–T1 interspace and the extradural space identified by the hanging drop method. Bupivacaine (0.37–0.4 %) 15 ml (and in most patients fentanyl 50–100 μg also) was administered into the extradural space, after negative aspiration for blood and a lignocaine test dose. The majority of patients needed supplementary sedation during the procedure but a large proportion (46 %) found the technique satisfactory. Complications in these experienced hands appeared to be few, the most frequent being cardiovascular: hypotension (affecting 10.9% of patients), bradycardia (2.8%) and extradural venepuncture (1.5%). The first two complications were treated with a vasopressor or atropine, respectively; the third led to one grand mal convulsion. Neurological deficit also occurred in a significant proportion of patients, but was detected very early and the incidence of permanent neurological deficit was correspondingly very low (3%). The mortality of the series was 2.3%, which compares well with North American statistics indicating a perioperative mortality of 2.8% [26].

Cervical extradural block does, therefore, appear to have a place in the performance of carotid endarterectomy. However, it should be stressed that experience of the technique is essential to prevent the highly dangerous complications which may occur occasionally. According to a recent survey [56], most British anaesthetists do not make use of this method of anaesthesia, but perhaps its use may increase in the future.

General anaesthesia

General anaesthesia is undoubtedly more familiar ground for the majority of anaesthetists. The choice of a specific technique is less important than the maintenance of adequate cerebral and coronary blood flows; this can be achieved by a variety of means. Oxygenation, the airway, systemic arterial pressure and blood carbon dioxide tensions may be controlled effectively under general anaesthesia, allowing the anaesthetist considerable influence over factors which improve surgical outcome; namely, cerebral blood flow and cerebral metabolism. Some degree of cerebral protection is another benefit of the carefully managed general anaesthetic.

In the 1960s and early 1970s it was believed that general anaesthesia with hypercapnia and induced hypertension was the preferred technique for carotid endarterectomy. The rationale for this approach was that general anaesthesia reduced $CMRo_2$ and increased the blood oxygen content by delivery of large inspired concentrations of oxygen. The increase in arterial pressure was thought to increase collateral blood flow and the hypercapnia to increase global cerebral blood flow. These factors, combined, were thought to provide cerebral protection. This technique has now been shown to be undesirable for two reasons. First, intracerebral steal may occur with the diversion of blood supply from compromised tissue to relatively normal tissue, leading to worsening hypoxic brain damage. Second, by the effects on the heart of increased carbon dioxide tensions concurrent cardiac work, myocardial compromise and arrhythmias may develop [7].

The control of arterial pressure, however, is important. Both hypotension and excess hypertension should be avoided during carotid endarterectomy. The former obviously leads to malperfusion of what could be critically perfused cerebral tissue with consequent neurological damage. This complication may be avoided by ensuring adequate hydration before and throughout the operation and avoiding the clumsy use of agents known to decrease arterial pressure. Extreme hypertension is also dangerous because of its deleterious demands upon the heart.

Attainable goals during surgery should be no systolic arterial pressure less than 100 mm Hg or a decrease greater than 40 mm Hg from the smallest preoperative systolic pressure in patients with known hypertension. Increased arterial pressure can be manipulated during operation by various means. Infusions of the ultra short-acting beta-adrenoceptor blocker, esmolol, have been used in the U.S.A. to control the hypertensive response to intubation, thus decreasing the need for increases in the concentration of anaesthetic agents which may then cause a precipitous decrease in arterial pressure when intubation has been accomplished [23]. A short-acting opioid, for example alfentanil, may also be used for this effect [52]. Because of the brief action of these drugs, decreases in arterial pressure encroaching into the intraoperative period are unlikely. During operation, application of a local anaesthetic to the carotid sinus prevents the hypertensive response to clamping of the vessel, but the anaesthetist should be prepared for a possible surge in arterial pressure and have the appropriate agents available.

What of induced hypertension? Blood vessels in ischaemic regions are thought to be in a maximally dilated state; thus they do not display autoregulation and are, therefore, "pressure dependent" and exquisitely sensitive to inadequate arterial pressure. There is, therefore, an argument that induced hypertension ensures a margin of safety for perfusion of these regions. Unfortunately, utilizing vasopressors to induce hypertension in this patient population increases cardiac afterload and myocardial oxygen consumption; we do not recommend that this technique be used. "Light" anaesthesia to achieve the same increases in arterial pressure is not associated with the same incidence of myocardial ischaemia and may be used by those in favour of the above rationale [79]. Occasionally, of course, unexpected decreases in arterial pressure occur despite adequate fluid volume and appropriate anaesthetic depth. Under these circumstances, the alpha-adrenoceptor stimulant, methoxamine, is probably the drug of choice as it vasoconstricts with minimal concurrent tachycardia and may be used to return the arterial pressure to the normal range.

Other anaesthetic techniques

Inhalation agents. All three volatile anaesthetics commonly in use today, halothane, enflurane and isoflurane, increase cerebral blood flow in man.

Halothane suppresses EEG activity only at doses not tolerated by the cardiovascular system. It is known also to increase the cerebral lactate:pyruvate ratio [53]. For these reasons, which together show halothane to be a poor suppressor of $CMRo_2$, it is better avoided for carotid endarterectomy.

Enflurane may, in large doses, and in the presence of hypocapnia, cause spike and dome complexes similar to those of clinical seizure activity so is better avoided, especially when EEG monitoring is in use. Investigations undertaken in the U.S.A. assessing critical regional cerebral blood flow during carotid endarterectomy with differing concentrations of halothane and 50% nitrous oxide in oxygen revealed that ischaemia occurred at flows less than 18–20 ml $min^{-1}/100$ g [75]. Similar critical flows were shown to exist for enflurane used in the same way [52].

Isoflurane, however, has been shown to allow a greater decrease in regional cerebral blood flow than the other two agents [52]. Patients anaesthetized with isoflurane, in appropriate concentrations, showed no evidence of cerebral ischaemia on the intraoperative EEG, and developed no new neurological deficits after operation when measured flows as small as 10 ml $min^{-1}/100$ g were shown to have occurred [50]. In addition, isoflurane at concentrations less than 1.5 MAC in an animal model produced less cerebral vasodilatation than halothane [86] and did not increase cerebral blood flow at 1.0 MAC in man [58], thus avoiding the problems associated with cerebral dilatation during carotid endarterectomy: increased intracranial pressure, cerebral steal phenomenon, or both.

By decreasing the probability of awareness during surgery and reducing requirements for long acting opioids, isoflurane, in concentrations less than 1.0 MAC, is the inhalation agent of choice. It would be tempting also to extrapolate from the above information that it has some cerebroprotective effects, but the belief that isoflurane protects the brain in a manner similar to barbiturate drugs is now considered unlikely [86, 88].

Nitrous oxide has been shown to have several deleterious effects in the setting of carotid surgery. An increase in intracranial pressure secondary to metabolic activation is associated with its use [39], the potential for air embolism is aggravated and it may negate the cerebroprotective effects of thiopentone [38]. These three factors suggest that an air–oxygen mixture combined with low-dose isoflurane may be the inhalation anaesthetic combination associated with fewest complications. Interestingly, propofol may obtund these metabolic effects of nitrous oxide [33] but, as discussed previously, has not been fully evaluated in the context of carotid surgery.

Opioid analgesics. The use of opioid analgesics is essential in the light of the previous discussion. The agents of choice are the newer synthetic opioids (fentanyl and alfentanil). Fentanyl, in particular, has a mild vasoconstrictive effect with an accompanying reduction in $CMRo_2$. Alfentanil may also have these effects, but must be titrated carefully to avoid unexpected hypotension when combined with other i.v. agents.

Neuromuscular blocking agents. Intubation of the trachea is essential, in order to guarantee security of the airway and permit mild hyperventilation. Either depolarizing or non-depolarizing neuromuscular blocking drugs may be used for tracheal intubation but, if suxamethonium is used, the possibility of hyperkalaemia in the paraplegic patient must not be overlooked [21]. Atracurium and vecuronium are the non-depolarizing drugs of choice as they are associated with greater cardiovascular stability than other agents. The new agent pipecuronium bromide may also be ideal for carotid endarterectomy, as it has a long duration of action and is associated with cardiovascular stability [74].

Postoperative Considerations

The postoperative sequelae of carotid endarterectomy may be varied and multiple. A physiological approach to understanding potential complications assists when considering their clinical management. This is never more important than for the cardiovascular system.

The complications of the pre- and perioperative periods pertaining to the heart and vascular tree apply equally to the postoperative phase. Lability of arterial pressure may lead to myocardial infarction, stroke or, less commonly, the hyperperfusion syndrome. The detection of myocardial infarction in the postoperative period relies on vigilance of the surgical team and some have advocated "myocardial surveillance" by serial ECG over the first 3 days after operation for early detection and subsequent management of myocardial infarction or ischaemia [20].

Hypertension

Neurological deficits are undoubtedly more common in the patient in whom control of arterial pressure is poor [72]. In the postoperative period, this may occur for a variety of reasons. Hypertension, defined as a systolic arterial pressure greater than 180 mm Hg or 40 mm Hg greater than preoperative values, or a diastolic arterial pressure greater than 100 mm Hg, may occur because of "wearing off" of preoperative medications, pain, agitation, new neurological deficit or dysfunction of the carotid sinus baroreceptor reflexes. The last of these results from interruption of carotid sinus innervation of the medullary vasomotor centre, which falsely indicates systemic hypotension. The reflex arc then results in an increase in sympathetic nervous activity and a vagolytic effect on the heart, with resulting hypertension and tachycardia.

Neurogenic hypertension may also occur, and is believed to be caused by deteriorating neurological state of the patient. In one study [45], 69% of patients with neurological deficits developed hypertension, whereas only 28% of neurologically intact patients did so. Thus hypertension occurring after carotid endarterectomy may serve as the first sign of impending deterioration in neurological function. Several hypotheses exist. Surgical manipulation of the carotid bulb may lead to a humoral influence on arterial pressure in addition to the reflex arc described above. Hodge, Lowe and Vane [41] noted increased angiotensin concentrations in dogs after bilateral carotid occlusion, presumably because of stimulation of renin release by sympathetic discharge. Total extradural anaesthesia, but not bilateral nephrectomy, blocked this increase in arterial pressure [55], suggesting that the sympathetic discharge was unrelated to the kidneys. Another possible mechanism accounting for a surge in arterial pressure in the postoperative period is that related to centrally acting sympathetic neuroamines such as noradrenaline or adrenaline. Ahn, Marcus and Moore investigated this issue [3] and found statistically significant increases in cerebral noradrenaline concentrations. They postulated that these existed as a result of increased release from intracranial capillary and arterial endplates in response to the hypoperfusion occurring during carotid cross-clamping. The same authors suggested that this central response may be inadequately treated by peripherally acting antihypertensive drugs.

The aetiology of hypertension in the postoperative period should, therefore, be considered before selection of a suitable therapeutic agent.

Management. Most clinicians appear to favour use of a short-acting antihypertensive given by infusion. Alteration of infusion according to response and rapid discontinuation of therapy if hypotension should occur unexpectedly are advantages of this approach. Sodium nitroprusside is an obvious drug of choice. By acting as both an arterial and venous vasodilator, and because of its extremely short onset and duration of action, it can be carefully titrated to effect by infusion. It does, however, suffer the disadvantages of association with tachyphylaxis and possible accumulation of thiocyanate if used for prolonged periods, and should therefore be replaced with longer acting vasodilators if required other than for 24–72 h control of arterial pressure.

The short acting beta-blocker, esmolol, also may be given by infusion for rapid control of heart rate and arterial pressure [23]. This drug may also be of benefit in counteracting the increases in renin, and consequently angiotensin, concentration as hypothesized by some authors [41]. Esmolol infusion should be replaced by longer acting oral or i.v. agents if prolonged medication is deemed necessary, as infusions of this agent are currently very expensive. Although less controllable than esmolol, labetalol (a combined alpha-and-beta adrenoceptor antagonist) is favoured by many for the short-term control of arterial pressure in the immediate postoperative period. It is usually given i.v. in repeated (if required) bolus doses.

Calcium channel blockers also may be used to achieve control of hypertension, particularly in the presence of myocardial ischaemia.

Finally, the central sympathomimetic theory of postoperative hypertension warrants trial of clonidine as a suitable antihypertensive drug [3]. This would be an interesting adjunct to current therapy, but remains to be thoroughly evaluated.

Hypotension

Unexpected hypotension may occur and is equally as hazardous as hypertension. It may result from relative hypovolaemia, oversedation or a differing response of the carotid sinus to increased flow (stretching of the receptors with a resulting hypotensive reflex).

Baroreceptor function does, however, decrease with increasing age and cerebrovascular disease and may not affect postoperative arterial pressure as much as expected. A simple test to evaluate baroreceptor function, performed easily before operation, is to ask the patient to perform a Valsalva manoeuvre. If no brady–tachycardiac response occurs, baroreceptor function is obviously not normal. In any event, hypotension can be treated satisfactorily by ensuring absence of hypovolaemia, myocardial ischaemia and oversedation and then by treating with a stimulant drug such as methoxamine, phenylephrine or ephedrine in incremental bolus doses until vasoconstriction restores a reasonable cerebral perfusion pressure.

Neurological deficit

Postoperative neurological deficit occurs in 1–7% of patients after carotid endarterectomy, regardless of anaesthetic technique [6]. Patients who are neurologically unstable before surgery or who have angiography which demonstrates soft thrombus, contralateral stenosis or extensive disease do suffer more frequent neurological problems. Treatment of a new neurological deficit may require immediate return to the operating theatre without performance of angiography [45]. Otherwise, management is by prevention: control of arterial pressure, good surgical technique, heparinization and avoidance of prolonged intraoperative clamping.

Hyperperfusion syndrome

The hyperperfusion syndrome is another complication of carotid endarterectomy. Because of the stenotic nature of the diseased carotid artery, the intracranial blood vessels supplied by that vessel are conditioned to receive minimal blood flow and are chronically vasodilated to maintain adequate cerebral perfusion. Their ability to autoregulate is lost. After carotid endarterectomy has restored normal perfusion pressure, a state of hyperperfusion exists at least until autoregulation is regained after some days [14]. This may present as migrainous type headache, seizures or unexpected intracerebral haemorrhage. Unfortunately, CT scan, angiography and clinical examination may demonstrate no abnormality in the early phases, but complaints of severe unilateral headache, with or without neurological deficit occurring up to 5 days after operation, should be taken seriously and control of arterial pressure commenced [67]. This is particularly important in those patients known to have high-grade stenosis, severe hypertension, or both, before operation, as they are at risk of this complication. Patients who have seizures without evidence of focal ischaemia (on CT scan) should be treated with anticonvulsants. Anticoagulation is contraindicated, as it may precipitate intracerebral haemorrhage. Perioperative antiplatelet therapy should also be used with caution for the same reasons.

Postoperative haemorrhage

Postoperative haemorrhage causing swelling of the neck may occur. Difficult intubation may result from this complication and the unwary may mismanage these patients with catastrophic results [61]. Clinical assessment of the airway can underestimate the potential hazard of a rapid sequence induction technique. Thus the necessity for general anaesthesia must be defined. Could surgical evacuation of the haematoma be performed under local anaesthesia? If a general anaesthetic is necessary, an inhalation induction or a fibreoptic awake intubation are the methods of choice.

RECOMMENDED GENERAL ANAESTHETIC TECHNIQUE

Anaesthesia for carotid endarterectomy presents a challenge for the anaesthetist. An understanding of the nature of the disease process, the surgical technique and the physiology of the cardiovascular and neurological systems is mandatory. Thorough cardiovascular and neurological preoperative assessment and management must take place and a suitable anaesthetic technique be considered. Two options are available—regional or general anaesthesia.

In the opinion of the authors, a suitable basic general anaesthetic technique would be as follows. The patient should be seen by the anaesthetist before surgery for full preoperative evaluation and discussion of the forthcoming procedure. Benzodiazepine premedication should be prescribed in a low dose; for example, diazepam 5–10 mg 1.5–2 h before the start of surgery or temazepam 20–30 mg by mouth 1–2 h before surgery.

Aids to intraoperative monitoring should be commenced in the anaesthetic room: ECG, non-invasive measurement of arterial pressure, intra-arterial catheter placement under local anaesthesia and all other monitors recommended by the Association of Anaesthetists of Great Britain and Ireland [2].

Induction should commence after 3 min of preoxygenation supplemented with i.v. midazolam through a large-gauge, free-flowing infusion, to produce a state of light sedation. Induction is then completed with thiopentone 5–7 mg kg^{-1} followed by an intubating dose of non-depolarizing neuromuscular blocker (suitable examples are vecuronium 0.1 mg kg^{-1} or atracurium 0.5 mg kg^{-1}). Tracheal intubation may be undertaken after adequate time for relaxation and after pretreatment with lignocaine 1 mg kg^{-1} i.v. or an infusion of esmolol commenced at 500 μg kg^{-1} min^{-1} or pretreatment with alfentanil 10 μg kg^{-1}. In this way surges in arterial pressure or intracranial pressure may be avoided.

Anaesthesia should be maintained with an oxygen–air mixture, isoflurane 1.0 MAC or less and supplementary doses of opioids such as fentanyl or alfentanil to provide a stable intraoperative course. Normocapnia (end-tidal carbon dioxide and confirmatory blood-gas measurement), normotension or hypertension within 20 % of the preoperative arterial pressure (not exceeding 200 mm Hg) and avoidance of hypovolaemia by adequate transfusion of colloids or blood are all desirable goals. Mild hypothermia to 34 °C may be an advantage. If a shunt is used, it may be worth considering the administration of thiopentone by infusion during the periods of clamping before insertion and removal of the shunt. Ideally, a burst suppression pattern should be obtained on the EEG. However, in practice, it may be better to ensure that arterial pressure is not compromised.

At the conclusion of surgery, antagonism of neuromuscular block should be achieved with neostigmine and glycopyrronium, and inhalation anaesthesia discontinued to allow a smooth but rapid awakening for evaluation of neurological status. Transfer to a neurosurgical intensive care unit would be undertaken when awakening is satisfactory. Supplementary oxygen should be given during transfer and continued into the postoperative period. The intensive care staff should be alerted to observe closely for fluctuations in arterial pressure outside pre-set limits, neurological deterioration, hypersomnolence, unilateral headache and presence of wound haematoma.

In addition to the basic technique of anaesthesia, it would be customary to consider techniques of monitoring directed specifically to the central nervous system or deliberate manipulation of cerebral metabolism. The advisability of this would depend on the individual patient, the extent of the disease process and the surgical technique used (e.g. shunt or no shunt).

COMMENT

The place of carotid endarterectomy as a surgical procedure is currently under scrutiny [35, 71, 84]. Medical therapy and the decreasing incidence of stroke in the general population have called into question the relevance of the operation. For example, Winslow and colleagues [91] concluded from their study in a random sample of 1302 patients undergoing carotid endarterectomy that only 35 % had the procedure for an appropriate reason. In their view, the reasons were equivocal in 32 % of patients and inappropriate in 32 %. However, the picture is now becoming clearer: several large-scale trials of carotid endarterectomy have recently issued preliminary reports. The European Carotid Surgery Trial (ECST) [30], which began in 1981, has studied the results from 2518 patients over the past 10 years. In those patients in whom there was a 30–69 % stenosis of the carotid artery, the balance of surgical risk and eventual benefit remains uncertain. The benefits of surgery were outweighed by the risks in patients with mild degrees of carotid stenosis (< 29 %). In contrast, however, the immediate risks of operation were significantly outweighed by the later benefits in the group of patients with severe stenosis (70–99 %). The North American Symptomatic Carotid Endarterectomy Trial (NASCET) [59, 60] began in 1988 and, after allocating more than 1000 patients randomly between surgery and non-surgery, has produced findings similar to those in the ECST investigation. In particular, NASCET demonstrated statistically definitive benefits of surgery in those patients with "severe" stenosis (70–99 %). The results for patients with moderate (30–69 %) stenosis remain unclear (as in ECST); however, random allocation of treatment for such patients is continuing.

The implications of these findings for the anaesthetist are clear. First, it is likely that only those patients with the "severest" degree of stenosis will be submitted for surgery. Obviously, this is a group of patients in whom the alterations to cerebrovascular physiology, and the results of anaesthetic manipulation, will be the most marked.

Second, at least as far as the U.K. is concerned, the results of the ECST study could suggest that there will be a 3–5-fold increase per annum in the number of carotid endarterectomies over the next decade [29].

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British Journal of Anaesthesia 1993; 71: 580–582

SHORT COMMUNICATIONS

CONTINUOUS SUBCUTANEOUS INFUSION OF MORPHINE—AN ALTERNATIVE TO EXTRADURAL MORPHINE FOR POSTOPERATIVE PAIN RELIEF

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SUMMARY

In a randomized, double-blind study of 40 patients undergoing total abdominal hysterectomy, we have compared continuous subcutaneous infusion (CSCI) of morphine with discontinuous extradural injection of morphine for postoperative analgesia at rest and during cough. The CSCI group received a bolus of morphine 0.1 mg kg^{-1} i.v. at the end of the operation and continued with s.c. infusion of morphine 30 µg kg^{-1} h^{-1}. The extradural group received morphine 4 mg extradurally at 0, 2, 10 and 18 h after operation. Pain and side effects were evaluated at 2, 4, 8, 12 and 24 h after operation. In the extradural group, significantly smaller pain-scores were observed both at rest and during cough compared with the CSCI group. No significant difference was observed between the groups regarding supplementary doses of morphine, peak expiratory flow values or side effects. We conclude that morphine by CSCI is not as effective as morphine injected extradurally. However, CSCI seems to provide simple and relatively effective analgesia with a low rate of side effects. (Br. J. Anaesth. 1993; **71**: 580–582)

KEY WORDS

Analgesics: morphine. Anaesthetic techniques: extradural, continuous subcutaneous infusion. Pain: postoperative. Surgery: abdominal hysterectomy.

Opioids injected into the extradural space produce effective and often prolonged analgesia. Unfortunately, there may be contraindications to placing an extradural catheter.

Because of both simplicity and familiarity with the technique, i.m. injections of opioids are very often used as an alternative to extradural opioids. However, there are many disadvantages of this method: the dose prescribed results in widely fluctuating plasma concentrations of the drug, i.m. injections are painful and the technique is time-consuming and induces a feeling of dependency on the nursing staff.

Continuous subcutaneous infusion (CSCI) of morphine may be a preferable alternative for patients without an extradural catheter. This method has been described as a simple and effective means of achieving postoperative analgesia after major surgery [1, 2]. This study was designed to establish the intensity of analgesia and frequency of side effects attributable to the use of morphine by CSCI and to compare the findings with those associated with the extradural administration of morphine.

METHODS AND RESULTS

We studied 40 patients, all ASA class I undergoing elective total abdominal hysterectomy, in a randomized, double-blind controlled study. Informed consent was obtained from each patient and the study was approved by the District Ethics Committee and the Danish National Health Service.

Before induction of general anaesthesia, all patients had an extradural catheter inserted between L2–3 or L3–4. After premedication with diazepam 10–20 mg by mouth, anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and pethidine 1 mg kg^{-1}. After precurarization with pancuronium 0.01 mg kg^{-1} and atropine 0.01 mg kg^{-1}, suxamethonium 1.5 mg kg^{-1} was used to facilitate orotracheal intubation. Anaesthesia was maintained with 0.25–1.0 % halothane and 67 % nitrous oxide in oxygen; supplementary doses of pethidine were given when needed.

Each patient was allocated randomly to one of two groups:

CSCI group. After closure of the peritoneum, a loading dose of morphine 0.1 mg kg^{-1} i.v. was given. Thereafter, an infusion of morphine 30 µg kg^{-1} h^{-1} s.c. was started via a 24-gauge needle placed above the pectoral muscle. Two, 10 and 18 h after the loading dose of morphine, isotonic sodium chloride 10 ml was injected extradurally.

Extradural group. After closure of the peritoneum, morphine 4 mg in isotonic sodium chloride 10 ml was injected extradurally. Thereafter, a 24-gauge needle was placed s.c. above the pectoral muscle and

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infusion of isotonic sodium chloride was started. Two, 10 and 18 h after the loading dose of extradural morphine, morphine 4 mg in isotonic sodium chloride 10 ml was injected extradurally.

In both groups, s.c. infusions were administered by a Travenol Infuser (Baxter Medical AB) at a fixed dose rate of 2 ml h^{-1}. After operation, morphine 0.05 mg kg^{-1} i.v. with no limitations on frequency was given if requested by the patient. Assessments were made 2, 4, 8, 12 and 24 h after operation. The severity of pain was assessed at rest and during cough, using a visual analogue scale (VAS) with values from 0 mm (no pain) to 100 mm (worst pain imaginable). Peak expiratory flow rate (PEFR) was measured. The level of consciousness was assessed on a four-point scale (from awake and oriented to not arousable). Side effects were monitored including respiratory depression, nausea, vomiting, pruritus and urinary retention. All patients remained in the intensive care unit for 24 h after the operation. Thereafter extradural or s.c. administration of morphine was stopped. For further postoperative analgesia in the ordinary ward, a fixed dose of morphine 5–10 mg was prescribed, and given on an as-required basis.

During the next 3 days, all patients were asked to note for how many hours they were mobilized (out of bed) and the onset of intestinal transit after the operation. Any postoperative complication and the duration of stay in hospital were noted.

Results are presented as median (range). The groups were compared for patient characteristics, duration of operation, intraoperative use of pethidine, bowel function and duration of hospital stay using the Mann–Whitney rank sum test for unpaired data. As the design implied multiple within-person assessments over time, analysis of variance was used. For intergroup comparison at specific times, we used a Mann–Whitney rank sum test for unpaired data with Bonferroni's correction. For time and the interaction between time and treatment we used the multiple comparison procedure based on the Friedmann test. $P < 0.05$ was considered as significant. The number of patients was chosen to ensure $2\alpha = 0.05$ and $\beta = 0.10$ with an effect of 10 mm on the VAS-score during cough. This gives approximately 15 patients in each group with an SD of 10 mm.

Three patients in the extradural group and four in the CSCI group were withdrawn because of procedural mistakes. The two groups were comparable in age, height, weight, duration of operation and peroperative use of pethidine (data not shown).

The pain scores were significantly smaller in the extradural group both at rest and during cough (fig. 1).

There was no difference between the two groups in requirement for supplementary analgesia (extradural group 1.8 doses per patient; CSCI group 3.2 doses per patient) or sedation score, although there was a tendency towards greater sedation scores in the CSCI group.

PEFR as percentage of preoperative value and the incidence of side effects did not differ significantly between groups.

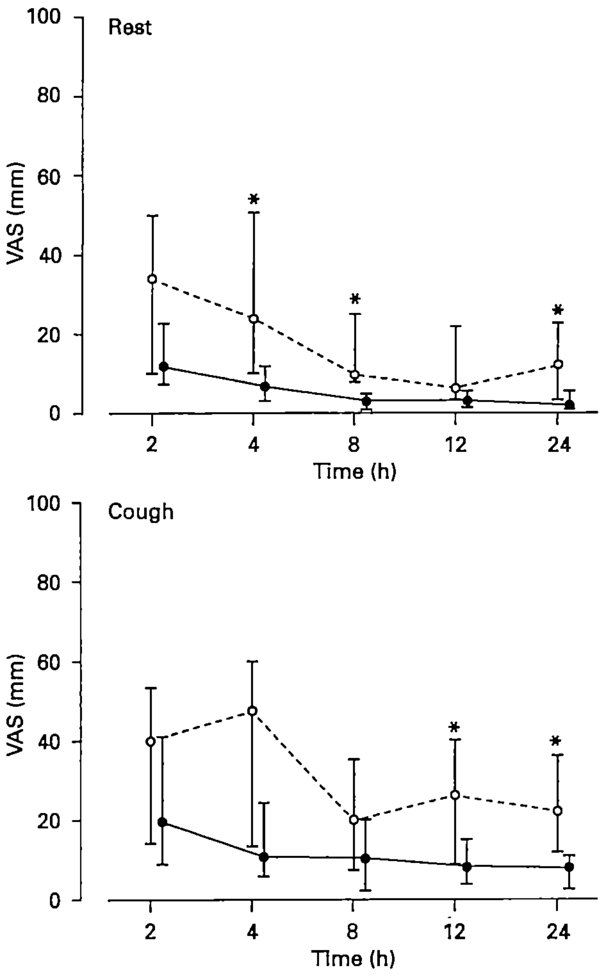

FIG. 1. Pain at rest and during cough in patients receiving continuous s.c. infusion of morphine 30 µg kg^{-1} h^{-1} (- - - -) or extradural injections of morphine 4 mg/8 h (——) (median values, upper and lower quartiles). $*P < 0.05$ between groups.

No signs or symptoms of intolerance or local toxicity developed in any patient at the site of the s.c. infusion. There were no cardiovascular or respiratory complications requiring treatment in any patient in the study.

There was no significant difference between groups in the times that elapsed before the first passage of flatus and faeces, the number of hours patients were mobilized or the duration of the postoperative stay in hospital.

COMMENT

We have found a significant difference in VAS-scores in favour of the extradural group compared with the CSCI group, both at rest and during cough. In the first 4 h after operation the VAS scores in the CSCI group were unsatisfactorily high. This is emphasized by the fact that 60% of the additional morphine required in the CSCI group during the study was given within these 4 h. A further improvement in these first VAS scores might have been achieved if a greater peroperative loading dose was used, but this may have increased the incidence of side effects.

Although it is difficult to compare different studies, it is noteworthy that much greater VAS scores have been reported after total abdominal hysterectomy using on-demand injections of opioids, compared with our results in the CSCI group [3, 4].

We found no significant difference between the groups in the two objective indices of pain severity. The lack of correlation between pain scores and opioid requirement is probably caused by the fact that some patients, for psychological or cultural reasons, have residual pain but do not ask for supplementary medication. The postoperative peak expiratory flow rates in the extradural group were constantly greater than those in the CSCI group, but this difference was not significant. In both groups, peak expiratory flows were significantly greater 8, 12 and 24 h after operation compared with the 2-h values.

We found no difference between the groups in the incidence of side effects. The tendency towards greater sedation in the CSCI group was not surprising and is in agreement with other studies comparing extradural and parenteral opioids [5].

There was no difference between groups in the time to first passage of flatus and faeces. This finding may have been influenced by the administration of morphine 5–10 mg in the ordinary ward.

Despite better pain relief and a tendency towards less sedation and better postoperative mobilization in the extradural group, these changes did not result in earlier discharge from hospital in these patients. However, discharge time is dependent on many other factors which could not be matched in this study.

Morphine by CSCI provided simple and relatively effective analgesia with a low rate of side effects. A major concern with this method of administration of opioids is irregular absorption from the subcutaneous depot because of uneven skin perfusion. However, it has been suggested that blood concentrations of morphine during CSCI are stable and not subject to sudden changes [2, 6]. We believe that morphine by CSCI should be considered as a suitable alternative method of postoperative analgesia after major abdominal surgery, particularly if there are contraindications to the use of an extradural regimen.

ACKNOWLEDGEMENT

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DEEP BODY TEMPERATURE DURING THE WARMING PHASE OF CARDIOPULMONARY BYPASS

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SUMMARY

We have compared deep body temperature (DBT) measured at the forehead with the core temperatures of the nasopharynx, oesophagus and rectum during the warming phase of cardiopulmonary bypass (CPB) (moderate hypothermia of 26.7–29.6 °C) in 12 patients. DBT was measured transcutaneously by an insulated thermistor probe that created an area of zero thermal flow between skin and subcutaneous tissue. The core temperatures measured at different sites lagged behind the increase in arterial blood temperature during warming. The trend was most marked with rectal temperature and least with oesophageal temperature. Among all measurements, the closest linear relationship was found between forehead DBT and nasopharyngeal core temperature (0.99 × nasopharyngeal temperature (°C) − 0.07; SEE = 0.53; r = 0.99; P < 0.0001). Forehead DBT measurement may be useful as a reliable non-invasive method of monitoring cerebral temperature during CPB. (Br. J. Anaesth. 1993; **71**: 583–585)

KEY WORDS

Heart: cardiopulmonary bypass. Surgery: cardiac. Measurement techniques: thermometry.

Although tympanic membrane and nasopharyngeal temperatures are considered to reflect cerebral temperature, damage to the tympanic membrane [1] and nasal bleeding [2] may occur and there may be errors when placement of the probe is imprecise. Fox and colleagues proposed non-invasive deep body thermometry that measured deep body temperature (DBT) from the skin surface by creating an area under an insulated thermistor probe of zero thermal flow between skin and subcutaneous tissue [3]. This device was later improved by covering the probe with a heated aluminum frame that prevented radial heat loss in the tissue under the probe [4]. Recently, however, it was suggested that deep body thermometry may not reflect the rapid changes in body temperature that occur during cardiopulmonary bypass (CPB) [2].

We have evaluated a currently available non-invasive deep body thermometry system by measuring DBT at the forehead and comparing values with core temperatures obtained simultaneously in the nasopharynx, oesophagus and rectum during the warming phase of CPB in 12 patients.

METHODS AND RESULTS

We studied 12 ASA II and III patients (six male) undergoing elective cardiac surgery for valvular heart disease. Institutional approval was obtained, and informed consent from each patient. The mean age of the patients was 52 yr (range 39–66 yr), mean weight 54 kg (range 34–75 kg) and mean height 154 cm (range 140–169 cm). Eleven patients had valve replacement and one had open mitral commissurotomy.

Premedication consisted of diazepam 5–10 mg orally and hyoscine 0.3–0.5 mg s.c. Anaesthesia was induced and maintained with fentanyl 30–100 $\mu g\ kg^{-1}$ and midazolam 20–40 mg i.v. Tracheal intubation was facilitated by neuromuscular block with vecuronium. The lungs were ventilated mechanically using 100% oxygen. Volatile anaesthetics were not used. Moderate hypothermia (26.7–29.6 °C) was maintained during CPB with pump flow of 2.0–2.5 litre $m^{-2}\ min^{-1}$. Warming was facilitated by active vasodilatation with prostaglandin E_1 25–50 $ng\ kg^{-1}\ min^{-1}$. The operating room temperature was maintained within the range 23.0–25.0 °C.

DBT was measured at the forehead with a 7-g, 2.5-cm diameter surface probe and a deep body thermometer (PD-31 and CORE TEMP model CTM-205, Terumo, Tokyo, Japan). The probe consisted of an insulated thermistor covered by a cast aluminum shell with a high thermal conductivity, in which an electrically controlled heater and a second thermistor were incorporated. The second thermistor measured the temperature of the aluminum frame. The two thermistors were connected by two bridges. Skin temperature and temperature difference signals were amplified; the latter controlled the electrical current to the heater so that the temperature of the frame equalled that of the skin under the probe.

After induction of anaesthesia, a DBT probe was secured to the midline of the forehead using double-faced adhesive tape, a nasopharyngeal probe was advanced a distance equal to that between the external meatus of the ear and the external naris, an oesophageal probe was placed at the location where

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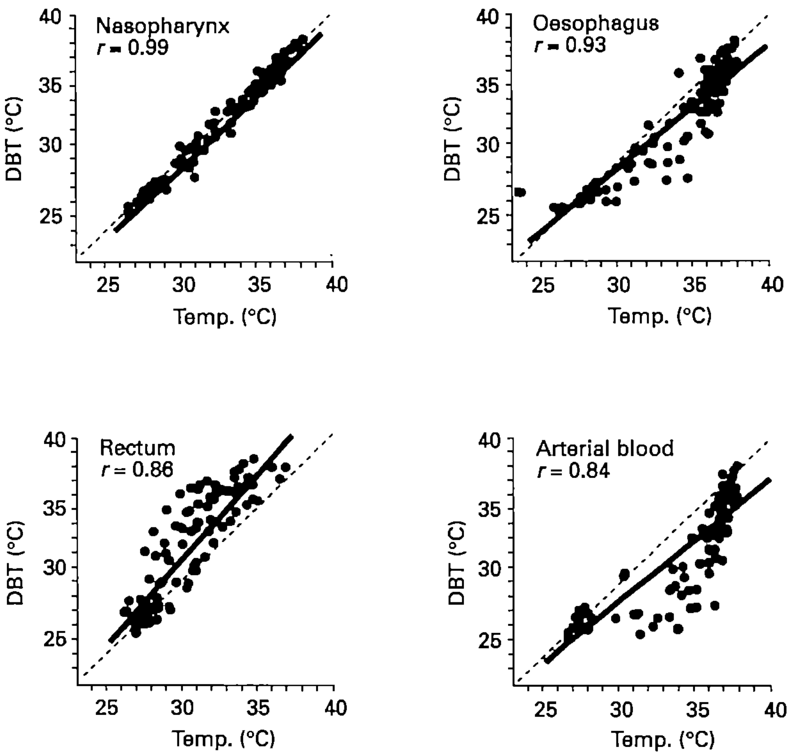

FIG. 1. Relationship of forehead deep body temperature (DBT) to nasopharyngeal, oesophageal and rectal core temperatures and arterial blood temperature during the warming phase of CPB. (------ = Line of identity).

the heart sounds were loudest and a rectal probe was advanced 10 cm. The nasopharyngeal, oesophageal and rectal probes were taped in position and were connected to a thermometer (TERUMOFINER, model CTM-303, Terumo, Tokyo, Japan). The temperatures were measured simultaneously eight or nine times for each patient during warming from 5 min before the arterial perfusate was warmed quickly to > 30 °C, until the discontinuation of CPB. The temperature of the oxygenated blood pumped into the aorta was considered to be the arterial blood temperature.

Values are expressed as mean (SD). The relationship between forehead DBT and other temperatures was assessed by correlation coefficient and linear regression analysis.

During the warming phase, arterial blood temperature increased from 27.9 (0.9) °C to 37.4 (0.4) °C. Pump flow increased from 2.1 (0.10) to 2.5 (0.03) litre m^{-2} min^{-1} and mean arterial pressure from 60 (13) to 65 (14) mm Hg.

Forehead DBT, nasopharyngeal temperature, oesophageal temperature and the rectal temperature increased at a slower rate than the arterial blood temperature (Ta) during warming. This trend was most marked with rectal temperature (0.49 × Ta (°C) + 13.62; $r = 0.67$; SEE = 1.94; $P < 0.0001$) and least with oesophageal temperature (0.99 × Ta (°C) − 0.78; $r = 0.92$; SEE = 1.48; $P < 0.0001$). The patterns of deviation from Ta of forehead DBT and nasopharyngeal temperature were similar (DBT, 0.87 × Ta (°C) + 2.38; $r = 0.84$; SEE = 1.99; $P <$ 0.0001 (fig. 1); nasopharyngeal temperature, 0.88 × Ta (°C) + 2.13; $r = 0.86$; SEE = 1.87; $P <$ 0.0001). In one patient, temperature was measured during hypothermia when cold cardioplegia solution was used. Oesophageal temperature registered 4 °C less than that of arterial blood. The temperature measured at other sites did not reflect the event.

Of the measurements made, the closest to linear relationship was found between forehead DBT and nasopharyngeal temperature (0.99 × nasopharyngeal temperature (°C) − 0.07; $r = 0.99$; SEE = 0.53; $P <$ 0.0001 (fig. 1)). The relationship of DBT to oesophageal and rectal temperatures was 0.89 × oesophageal temperature (°C) + 2.67; $r = 0.93$; SEE = 1.40; $P < 0.0001$ and 1.22 × rectal temperature (°C) − 4.91; $r = 0.86$; SEE = 1.86; $P < 0.0001$.

COMMENT

In this study, core temperature measured at different sites lagged behind the increase in arterial blood temperature during the warming period of CPB. Rectal temperature was slowest in reflecting arterial blood temperature changes, responses of nasopharyngeal temperature and forehead DBT were intermediate in speed and oesophageal temperature lagged least behind changes in arterial blood temperature. Of all the measurements of core temperature, the closest and directly linear relationship was found between forehead DBT and nasopharyngeal temperature.

Core temperature is considered to be the temperature of the central core of the body, within which temperature fluctuates minimally. The core is covered by the skin and subcutaneous tissues, through which temperature gradients exist. Core temperature is maintained nearly constant by active thermoregulation in the peripheral tissues against cold and warm environments. Although core temperatures measured at different sites are similar in unanaesthetized subjects or anaesthetized subjects in a steady state, surface temperature measured on the forehead is approximately 2 °C less than the core temperature and varies widely because of thermoregulation [5].

The DBT device, as described by Muravchick, exteriorizes core temperature [2]. The current device reduces radial thermal flow markedly in the tissues under the probe by heating the aluminium frame that covers an insulated thermistor to the same temperature as the thermistor and the reduction in the radial heat flow allows the region of zero thermal flow under the probe to enlarge [4]. Clinical trials have shown that the agreement between DBT and core temperature measured by conventional methods was good and that DBT tends to be 0.05–0.2 °C less than the core temperature measured by other methods [3, 4]. When an initial temperature equilibrium was attained between the insulated thermistor and deep tissues, DBT responded rapidly and followed the changes in core temperature closely when an endogenous pyrogen was injected i.v. [3]. DBT measured over the biceps also closely mirrored the rapid increase in muscle temperature measured by an i.m. thermocouple during isometric exercise [4]. The transcutaneous DBT measurement, thus, was thought to be a satisfactory continuous monitor of core temperature [4].

A large difference between forehead DBT and nasopharyngeal temperature has been reported during the rapid cooling and warming phases of CPB [2]. The DBT lagged behind nasopharyngeal temperature during cooling, but the difference was not predictable during warming: DBT lagged behind in some subjects, but increased ahead of nasopharyngeal temperature in others. In contrast, forehead DBT closely followed nasopharyngeal temperature in our study. The cause for this difference in the findings is not clear. During rapid changes in body temperature, regional temperature gradients may develop in core organs, depending on the differences in size, thermal conductivity and heat capacity of and arterial blood flow to the organs. As uniform changes in temperature of tissues depend on an even distribution of temperature in the tissues, the regional gradients may cause temperature discrepancies in different tissues measured. However, the non-systematic differences demonstrated appear to suggest that the difference between Muravchick's findings and ours may have been a result of mechanical rather than physiological causes. In our study, the probe was smaller and weighed less, and a headstrap was not used to secure the probe on the forehead. Excessive pressure may interfere with circulation to the tissue under the probe when perfusion pressure is reduced. Uneven pressure exerted on the frame of the probe may change the distribution of arterial blood flow under the probe, which may have accounted for a greater temperature under the probe.

The mechanism for the identical responses found in this study of forehead DBT and nasopharyngeal temperature during the warming phase of CPB may have been the similarity in the pattern of arterial blood supply to and the proximity of the measurement sites. The forehead area and the posterior and lateral walls of the nasopharynx receive a rich supply of arterial blood from the external carotid artery. The forehead also receives an arterial supply from the internal carotid artery through the supraorbital arteries. As reported previously [2, 6], the oesophageal temperature in this study tended to reflect the temperature of mediastinal structures during warming, and the rectal temperature showed a marked delay in changes in arterial blood temperature, presumably secondary to a relatively smaller arterial blood flow and possibly to the conduction of heat from a large amount of tissues surrounding the rectum. Prostaglandin E_1 used during the warming phase may also have helped to equalize the temperature in the nasopharynx and the forehead by active vasodilatation.

DBT measurement is a non-invasive procedure. The response of the probe was rapid and the forehead DBT closely followed the changes in nasopharyngeal temperature during rapid warming; thus DBT measurement may be a reliable, non-invasive method of monitoring cerebral temperature during CPB.

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British Journal of Anaesthesia 1993; 71: 586–588

HAEMODYNAMIC EFFECTS OF PROPOFOL DURING CORONARY ARTERY BYPASS SURGERY

A. PENSADO, N. MOLINS AND J. ALVAREZ

SUMMARY

We have studied the haemodynamic effects of a bolus injection of propofol 2 mg kg^{-1} in 20 patients with good ventricular function undergoing aorto-coronary bypass surgery. Heart rate and systolic and diastolic systemic (SAP, DAP) and pulmonary arterial pressures, central venous pressure, pulmonary artery wedge pressure, cardiac output (CO), right ventricular ejection fraction, systemic (SVR) and pulmonary vascular resistances and left ventricular stroke work index (LVSWI) were measured before and at 1, 3, 5, 10, 20 and 30 min after the administration of propofol. At 1 min, maximum decreases were detected in SAP (−26%, $P < 0.001$*), DAP (−17%,* $P < 0.001$*), SVR (−22%,* $P < 0.001$*) and LVSWI (−23%,* $P < 0.001$*). The other variables studied showed no significant variations at any time during the study. We conclude that propofol reduces systemic arterial pressure by a decrease in SVR, but not in CO or ventricular filling pressures.* (Br. J. Anaesth. 1993; **71**: 586–588)

KEY WORDS

Anaesthetics, intravenous: propofol. Anaesthesia: cardiovascular. Cardiovascular system: effects.

The decrease in arterial pressure produced during anaesthetic induction with propofol has been attributed to decreases in systemic vascular resistance (SVR) [1] and in cardiac output (CO) [2], the latter as a result of a direct negative inotropic effect of the drug [3] or a reduction in preload because of venodilatation [4]. We have studied the haemodynamic effects of a bolus dose of propofol in patients with coronary artery disease but good ventricular function during myocardial revascularization surgery, and its effect on right ventricular ejection fraction (RVEF) and on pressure–rate quotient (PRQ).

METHODS AND RESULTS

With Ethics Committee Approval, we studied 20 patients (one female), mean age 54.5 yr (range 41–77 yr), weight 76.2 (SD 10.6) kg and body surface area 1.85 (0.17) m^2, undergoing myocardial revascularization surgery. All patients had an ejection fraction > 0.5 and a left-ventricular end-diastolic pressure < 12 mm Hg. Internal mammary artery bypass was performed in all patients and haemodynamic measurements were obtained during dissection of the artery. Eleven patients had suffered previous myocardial infarction, one of them on two occasions. None of the patients had clinical evidence of unstable angina. Preoperative treatment consisted of calcium channel blocking drugs (13 patients), beta adrenoceptor blocking drugs (11 patients) and nitrates (six patients), and was continued until the morning of surgery.

The patients were premedicated with i.m. morphine 0.1 mg kg^{-1} and hyoscine 0.3 mg and oral diazepam 10 mg 1 h before surgery.

In the operating room, ECG (leads II and V_5) and arterial oxygen saturation (pulse oximetry) were displayed continuously. A radial artery and two peripheral venous cannulae were inserted. Anaesthesia was induced with etomidate 0.2 mg kg^{-1}, midazolam 0.1 mg kg^{-1}, fentanyl 10 μg kg^{-1} and pancuronium 0.1 mg kg^{-1}. After orotracheal intubation, the patient's lungs were ventilated mechanically with an oxygen–air mixture (FI_{O_2} 0.5) to achieve an end-tidal PCO_2 of 4–4.7 kPa. A pulmonary artery catheter was inserted via the right internal jugular vein (REF-1, Baxter Healthcare Corporation, American Edwards Laboratories). ECG and systemic and pulmonary arterial pressures were displayed continuously and central venous pressure (CVP) and pulmonary artery wedge pressure (PAWP) intermittently, using calibrated transducers with the right atrium as the reference point.

Anaesthesia was maintained with fentanyl i.v. to a total of 40 μg kg^{-1} at the moment of propofol administration, and isoflurane supplementation of up to 1% of the inhaled gas, according to clinical criteria. The last dose of fentanyl (10 μg kg^{-1}) was given to all patients and isoflurane discontinued 10 min before the haemodynamic study. No other drug, with the exception of propofol, was administered until the end of the study. At the start of the dissection of the internal mammary artery, it was verified in each patient that the end-tidal concentration of isoflurane was 0%. Until that time, fluid balance was maintained using Ringer's lactate

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TABLE I. *Heart rate (HR), systolic, mean and diastolic systemic arterial pressures (SAP, MAP and DAP), systolic and diastolic pulmonary arterial pressures (SPAP and DPAP), central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), right ventricular ejection fraction (RVEF), systemic and pulmonary vascular resistance (SVR and PVR), left ventricular stroke work index (LVSWI), and pressure–rate quotient (PRQ) before (Baseline) and 1, 3, 5, 10, 20 and 30 min after the administration of propofol 2 mg kg⁻¹ (mean (SD)). *P < 0.05; **P < 0.01, ***P < 0.001 compared with baseline*

	Baseline	1 min	3 min	5 min	10 min	20 min	30 min
HR (beat min^{-1})	68 (11)	70 (12)	66 (12)	65 (11)	64 (11)	64 (10)	66 (11)
SAP (mm Hg)	139 (11)	103 (11)***	111 (12)***	110 (11)***	115 (13)***	117 (15)**	122 (14)**
MAP (mm Hg)	92 (9)	75 (8)***	77 (9)***	77 (8)***	79 (8)***	79 (12)**	81 (10)**
DAP (mm Hg)	69 (7)	57 (8)***	61 (9)**	60 (8)**	63 (9)**	62 (10)**	65 (9)*
SPAP (mm Hg)	22 (5)	22 (6)	21 (6)	21 (6)	21 (5)	21 (6)	21 (6)
DPAP (mm Hg)	12 (6)	12 (6)	12 (5)	12 (5)	12 (5)	11 (6)*	11 (5)
CVP (mm Hg)	8 (5)	8 (5)	8 (5)	8 (5)	8 (5)	8 (5)	8 (5)
PAWP (mm Hg)	11 (6)	11 (5)	11 (5)	11 (5)	11 (6)	11 (6)	11 (6)
CO (litre min^{-1})	4.9 (0.9)	5.1 (1.2)	4.9 (1.2)	5.0 (1.0)	5.0 (1.0)	4.9 (1.0)	4.9 (1.3)
RVEF	0.49 (0.10)	0.47 (0.10)	0.47 (0.11)	0.50 (0.08)	0.48 (0.10)	0.50 (0.08)	0.50 (0.10)
SVR (dyn s cm^{-5})	1409 (268)	1106 (308)***	1200 (367)*	1146 (329)*	1197 (312)*	1215 (323)	1271 (379)
PVR (dyn s cm^{-5})	95 (42)	87 (37)	85 (46)	87 (36)	90 (30)	88 (39)	77 (42)
LVSWI (g m m^{-2} $beat^{-1}$)	44 (8)	34 (10)***	36 (9)*	38 (7)	40 (10)	39 (8)	39 (9)
PRQ (mm Hg min $beat^{-1}$)	1.39 (0.24)	1.09 (0.23)***	1.21 (0.27)**	1.22 (0.25)**	1.26 (0.27)*	1.25 (0.27)	1.26 (0.25)

solution 12 ml kg^{-1} and 3.5% gelatin solution 7 ml kg^{-1}.

The following variables were recorded as baseline: heart rate (HR), systolic, mean and diastolic arterial pressure (SAP, MAP and DAP), systolic and diastolic pulmonary arterial pressure (SPAP and DPAP), CVP, PAWP, CO and RVEF by thermodilution (REF-1, Ejection Fraction/Cardiac Output Computer). Propofol 2 mg kg^{-1} was then injected over 1 min, and the same variables were assessed at 1, 3, 5, 10, 20 and 30 min. SVR, pulmonary vascular resistance (PVR) and left ventricular stroke work index (LVSWI) were derived using standard formulae.

During the study, the presence of myocardial ischaemia was assumed if there was ST-depression of 0.1 mV in V_5 or 0.2 mV in lead II, or both, and increased PAWP or the appearance of prominent v-waves. In addition, PRQ ($MAP \times HR^{-1}$) [5] was calculated.

For statistical analysis, each measurement was compared with baseline using the Wilcoxon test for paired data, applying Bonferroni's correction for multiple comparisons. $P < 0.05$ was considered statistically significant.

The administration of propofol 2 mg kg^{-1} produced a maximum decrease in SAP, MAP and DAP after the first 1 min (−26%, −19% and −17%, respectively) ($P < 0.001$), which remained statistically significant throughout the entire study. The maximum decreases in SVR and LVSWI were recorded at 1 min (−22% and −23%) ($P < 0.001$) and remained significant until 10 min and 3 min, respectively. The rest of the variables studied underwent no significant changes in our study, with the exception of the DPAP at 20 min ($P < 0.05$) (table I).

There was no evidence of myocardial ischaemia in any of the patients during the study. PRQ was reduced from the first 1 min (−22%) ($P < 0.001$) and remained significantly decreased until 10 min (table I).

COMMENT

I.v. administration of propofol 2 mg kg^{-1} to patients with good ventricular function during the dissection of the internal mammary artery in aortocoronary bypass surgery produced a significant decrease in systemic arterial pressure that persisted throughout the 30-min duration of the study. This decrease was the result of a reduction in SVR rather than changes in CO or ventricular filling pressures.

This study was performed in patients subjected to minimal surgical stimulus, who were already under the effects of other anaesthetic drugs. Although we cannot exclude the possibility that these agents may have modified the haemodynamic changes associated with propofol, the basal values and all those recorded until the end of the study were obtained under the same conditions, and the changes observed must be attributed to the new drug and may apply to other clinical situations. In contrast, administration of the drug to anaesthetized patients with moderate hypocapnia eliminates the influence of the surgical stimulus, tracheal intubation, loss of consciousness or hypercapnia and respiratory acidosis observed in other studies [1]. Haemodynamic stability in our patients was assured, as sternotomy had been performed at least 15 min before the study, and the only response to isoflurane withdrawal and fentanyl administration was a slight decrease in HR which returned to baseline within a few minutes.

Our study confirms the lack of significant changes in HR after administration of propofol [1, 2]. It has been shown that propofol produces a resetting of the baroreflex mechanisms that enables a reduced HR to be sustained despite decreased arterial pressure [6]. It has also been shown that the addition of fentanyl significantly potentiates the effects of propofol on arterial pressure and HR [2]. Despite the fact that we used large doses of this opioid ($40\ \mu g\ kg^{-1}$), we did not observe these effects.

We have shown that there was a significant decrease in SVR lasting 10 min after propofol injection. Others have reported reductions in SVR of nearly 50 % with respect to basal values 5 min after administration of the drug in patients with artificial hearts and constant CO [4], suggesting a direct action of propofol on resistance vessels. The same work also demonstrated that propofol significantly reduces the preload of the right ventricle, suggesting a venodilator effect [4]. However, in our study, previous administration of crystalloids and colloids explains the stability of CVP and PAWP.

A decrease in SVR while PAWP remains constant, with no increase in CO, is commonly accepted as a sign of myocardial depression. The decrease in LVSWI observed partially counteracts the negative inotropic effect of propofol which is suggested in our report. Others had shown that the cardiodepressant effect of propofol may be prolonged and recovery may not parallel the anticipated decrease in plasma concentrations of propofol [3]. This could explain the fact that in our patients, who were subjected to a minimal stimulus, the haemodynamic effects of a single dose of propofol persisted for some time beyond the mean distribution life of the drug (1.8–4.7 min). It is interesting that the SAP, MAP and DAP remained significantly reduced after 30 min and it would be valuable to know the time required for it to return to baseline, but the design of our study did not permit us to assess this aspect.

We found no signs of myocardial ischaemia at any time during the study in spite of the fact that PRQ decreased significantly from 1 min to 10 min and approached the critical value of 1, which represents the cut-off point for an increased risk of ischaemia. In this respect, the absence of tachycardia to compensate for arterial hypotension produced by propofol prevents an increase in the demand for myocardial oxygen at a time in which the oxygen supply may be reduced.

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CASE REPORTS

FAILURE TO WEAN FROM CARDIOPULMONARY BYPASS AFTER MYOCARDIAL REVASCULARIZATION: SUCCESSFUL TREATMENT WITH VERAPAMIL VIA THE AORTIC ROOT

A. M.-H. HO, A. PARISI AND B. W. SHRAGGE

SUMMARY

Severe ventricular dysfunction in a patient prevented weaning from cardiopulmonary bypass after myocardial revascularization. Calcium chloride and increasing doses of dopamine had no effect. Coronary vasospasm was diagnosed based on ST elevation and myocardial failure. Verapamil 0.5 mg, injected into the aortic root, was followed by a dramatic improvement in cardiac contractility and successful weaning from cardiopulmonary bypass without inotropic support (Br. J. Anaesth. 1993; **71**: 589–591)

KEY WORDS

Heart: coronary vasospasm, verapamil. Surgery: cardiovascular.

Coronary vasospasm is an important cause of circulatory collapse after successful coronary artery bypass grafting. It may involve internal mammary artery [1–3] and saphenous vein [4, 5] grafts, in addition to native coronary arteries [2, 4, 6–8]. The phenomenon may be observed at any time during and shortly after cardiopulmonary bypass (CPB) [3, 5, 9], in the immediate postoperative period [1–3, 6, 10] and weeks [11] to months [11, 12] after surgery. Detailed reports on coronary vasospasm as a cause of inability to wean a patient from CPB are rare [8, 9]. In one patient [8] spasm persisted despite intracoronary infusion of nitroglycerin 8 mg, but was apparently relieved after nifedipine 30 mg was given via a nasogastric tube. The patient suffered a myocardial infarction. In another report [9], spasm occurred after injection of calcium chloride and was relieved by i.v. nitroglycerin. We are unaware of any report of the use of aortic root injection of verapamil to overcome coronary vasospasm and allow discontinuation of CPB. In the patient reported here, verapamil 0.5 mg relieved the spasm and profound myocardial dysfunction promptly and completely.

CASE REPORT

A 53-yr-old, obese male (101 kg) presented with angina pectoris precipitated by minimal exertion and after heavy meals, unresponsive to nitroglycerin spray, atenolol and aspirin. He had suffered a myocardial infarction 8 months previously. There was no history of vasospastic angina or intake of calcium channel antagonist. Coronary angiography revealed 70–80% stenosis of the right coronary (dominant), left main and left anterior descending arteries. The left ventricle was moderately hypokinetic and there was no valvular disease.

On the morning of the patient's planned coronary bypass surgery (CABG), he received his usual dose of atenolol and was sedated. In the operating room, routine monitors and a pulmonary artery catheter were placed. Anaesthesia was induced with fentanyl 75 μg kg^{-1} and vecuronium 0.1 mg kg^{-1} was given to facilitate tracheal intubation. The heart rate was increased with pancuronium 5 mg to 55 ± 3 beat min^{-1}. Pulmonary capillary wedge pressure (PCWP) was stable at about 12 mm Hg. Cardiac index was 3.3 litre min^{-1} m^{-2}. Before CPB was commenced, there were three spontaneous and apparently unprovoked episodes of systemic hypotension (systolic pressure 80–85 mm Hg) accompanied by 2–3 mm ST elevation in lead II, an increase in PCWP to 32–35 mm Hg, and the presence of the prominent V waves of mitral regurgitation. All episodes were promptly reversed with small i.v. doses of nitroglycerin, dopamine and phenylephrine.

The left internal mammary artery and saphenous vein were mobilized and wrapped in papaverine-soaked gauze. The vein was also filled with heparinized blood containing papaverine. Subsequently, CPB was initiated smoothly and asystole was achieved throughout the CPB period with cardioplegia solution (Na 140, K 20, Mg 3, Ca 2, Cl 115, acetate 27, gluconate 23 and tromethamine 5.1 mmol $litre^{-1}$; hydrocortisone 100 mg $litre^{-1}$) and hypothermia (28 °C). Saphenous vein grafts were anastomosed to the distal posterolateral circumflex artery and the right coronary artery, and the internal mammary artery was grafted to the left anterior descending artery. Total aortic cross-clamp time was 74 min. Phenylephrine 100 μg was given 20 min from the initial aortic cross-clamp for arterial pressure regulation. A small dose of nitroglycerin was given during the re-warming phase. Normal sinus rhythm and normothermia were achieved and the relatively empty heart was allowed to beat for 30 min. Cardiac contractions were very poor.

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An attempt was made to discontinue CPB by occlusion of the venous cannula, transfusion and the administration of calcium chloride 1 g i.v. (given routinely at this stage in our institution, unless the bypass time was very short and cardiac contractility obviously excellent). This resulted in overdistension of the ventricles, 4-mm ST-segment elevation in lead II, markedly increased pulmonary arterial pressures, markedly reduced systemic pulse pressure and poor pumping action by the ventricles. The severe hypokinesis, in marked contrast to the pre-CPB state, showed no improvement with the addition of dopamine 5 $\mu g\ kg^{-1}\ min^{-1}$. CPB was promptly re-instituted.

Another attempt at weaning from CPB 30 min later was again unsuccessful. No calcium chloride was given at this and subsequent attempts. An intra-aortic balloon pump (IABP) and a left atrial catheter were inserted. After another 1 h of CPB, a third attempt at weaning resulted in failure. CPB was re-instituted for the fourth time.

In view of the widespread ST changes consistent with coronary vasospasm, verapamil 0.5 mg in saline 1 ml was then injected into the aortic root. One minute later, another attempt at weaning was successful, without the use of any inotropic support. Ventricular contraction was vigorous and the systolic pressure > 100 mm Hg, while the left- and right-sided filling pressures remained decreased (13–17 mm Hg). The ST changes largely resolved and an infusion of verapamil 1 mg h^{-1} was commenced. Nitroglycerin was used after injection of protamine to allow transfusion of pump and other fluids into the patient. The final cardiac index was 3.4 litre $min^{-1}\ m^{-2}$. The remainder of the surgery was uneventful.

In the Intensive Care Unit, the patient was given verapamil 1–2 mg h^{-1} and hypertension was treated with nitroglycerin as required. Cardiac performance was deemed satisfactory even when the IABP was not used. There were no further episodes of coronary vasospasm and the IABP was discontinued 2 days later. Cardiac enzymes were not measured after operation. Except for pneumonia and confusion in the Intensive Care Unit, the remainder of the postoperative course was uneventful. The patient was discharged 10 days after surgery and remained angina-free and had continued to take atenolol and aspirin, but no calcium antagonist, during 14 months of follow-up.

DISCUSSION

The mechanisms of severe deterioration of myocardial function when weaning from CPB include [13] poor myocardial protection, excessive oxygen demand and decreased oxygen supply. Myocardial protection in this patient was performed with a standard technique used in thousands of successful cases in this institution, and probably elsewhere. We have no reason to believe the technique to have been inadequate. Conditions that cause excessive oxygen demand (hypertension and tachycardia) were absent. A primary decrease in oxygen supply was thus probably responsible. Laboratory measurements throughout the case excluded hypoxaemia and anaemia. Coronary insufficiency as a result of inadequate revascularization or diffuse stenosis was not the cause. Coronary air embolism may occur soon after unclamping of the aorta with the resumption of cardiac contractions, but it usually disperses quickly with adequate coronary perfusion pressure and rarely recurs [13]. The persistent and unrelenting nature of the ischaemia in this patient does not support air embolism as the major culprit, but it is difficult to exclude embolism or thrombosis as a contributory factor, although the relatively small PCV and impaired haemostatic properties of the blood after CPB do not promote thrombus formation. Our patient, a Caucasian, was unlikely to have had sickle cell disease. The most convincing evidence suggesting that coronary vasospasm was the dominant cause of this patient's profound ventricular failure was the rapid resolution of myocardial dysfunction and ischaemic changes immediately after the injection of verapamil.

The reported incidence of recognized coronary vasospasm (about 0.8–2.5% [7, 13]) is in keeping with our experience. Spasm is usually recognized because of its catastrophic presentation. It was responsible for six of 19 cases (32%) of sudden circulatory collapse after myocardial revascularization in one study [7], while Holter monitoring for at least 12 h after operation revealed an 8% incidence of ST elevation consistent with coronary vasospasm in another [14]. Less severe spasm may be missed and unreported [15]. We propose that the following factors may play a preventive role; routine continuation of nitrates and calcium antagonists before operation on the day of surgery; the use of high-dose opioid anaesthesia; routine wrapping of vessels in papaverine-soaked gauze and the use of papaverine-containing blood to fill the vessels before grafting; the presence of magnesium in the cardioplegic solution; the perfusion of the coronary arteries with warm cardioplegia solution towards the end of CPB; the administration of nitroglycerin towards the end of CPB; and the treatment of perioperative hypertension with nitrates.

The cause of coronary vasospasm associated with CPB is unknown. Many factors have been proposed [7–9, 13]: excessive alpha adrenergic stimulation, beta adrenergic block, alkalosis and reduced Pa_{CO_2}, cold, local trauma, release of vasoconstrictor substances from the endothelium, ischaemia, release of vasoconstrictor substances by platelets, increased concentration of potassium, reduced extracellular magnesium concentration, sudden increase in extracellular calcium, increase in plasma vasopressin concentration, vasodilator and calcium antagonist withdrawal, administration of protamine or transfusion-induced histamine liberation causing an H_1-receptor mediated coronary vasoconstriction, and an increased thrombin concentration upon heparin antagonism with protamine. The relative importance of these factors is unknown. Our patient had three probable episodes of spasm before CPB, suggesting the presence of triggering factors and susceptibility. The recurrence of spasm in a much more severe fashion after coronary artery bypass suggests that surgical manipulation, hypothermic CPB, or both, had contributed to the problem. It is possible that the phenylephrine used in the early phase of CPB in this patient contributed. The ventricles were functioning poorly before calcium chloride was given, but the drug did not help and could possibly have exacerbated the spasm [9].

Coronary vasospasm should be part of the differential diagnosis of ischaemia after CPB, irrespective of the presence or absence of preoperative Prinzmetal's angina and the type of vessel used for grafting. Recognition is by ST segment elevation or, less frequently, ST depression [4,5,16] accompanied by decreased contractility, arrhythmias, or both. When spasm occurs in isolated epicardial vessels, the surgeon should locate it by carefully examining the coronary vessels when and where possible, and should also palpate or inspect for suspected areas of akinesis or dyskinesis that had not been present before.

The treatment of coronary vasospasm is with vasodilators and avoidance of exacerbating factors whenever possible. I.v. nifedipine and nitroglycerin [8,9,13] are successful only occasionally, and may worsen hypotension. When circulatory collapse occurs with spasm after the chest is closed, or in the intensive care unit, cardiac massage may necessitate re-opening of the sternotomy site. When bedside resuscitation is unsatisfactory, return to the operating room for re-establishment of anticoagulation and CPB has been life saving. The intracoronary infusion of verapamil [6], nitroglycerin [6], or papaverine [2] by a cardiologist in the catheterization laboratory has been successful also. When spasm occurs while the patient is still on the operating table with the chest open, treatment will include one or more of the following: re-institution of CPB; administration of a calcium channel antagonist [10]; coronary perfusion with papaverine [3], nitroglycerin [5] or a calcium antagonist by aortic root or direct coronary injection; i.v. nitroglycerin [8]; the replacement of spastic coronary vessels with new grafts; the direct application of papaverine to the spastic vessel [1]; and avoidance of conditions that exacerbate coronary vasospasm.

Many inotropes and vasopressors (calcium chloride, dopamine, adrenaline, phenylephrine) may exacerbate coronary vasospasm. In the face of myocardial depression, the natural tendency is to increase the doses of these agents; this seems unlikely to succeed if the primary problem of spasm is ignored [5]. We feel, nevertheless, that judicious use of inotropes and vasopressors is probably not contraindicated absolutely. The use of IABP should be considered early. In severe spasm, however, that alone is unlikely to be sufficient.

Because of the global nature of ventricular dysfunction in our patient, we felt that coronary vasospasm was probably widespread. Rather than injecting verapamil into each individual coronary vessel, we decided to inject into the aortic root. Verapamil prolongs A–V node conduction and thus may add to the effect of hyperkalaemia. It is probably prudent to give an infusion of verapamil after the initial relief of coronary vasospasm, as recurrence is well documented [7, 8].

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SURGICAL EMPHYSEMA AND UPPER AIRWAY OBSTRUCTION COMPLICATING RECOVERY FROM ANAESTHESIA

M. C. BELLAMY, J. C. BERRIDGE AND S. S. M. HUSSAIN

SUMMARY

We describe a case of surgical emphysema and life-threatening airway obstruction resulting from a small pharyngeal perforation. The perforation apparently resulted from the use of a Yankauer-type sucker after uneventful anaesthesia for stapedectomy. (Br. J. Anaesth. 1993; **71**: 592–593)

KEY WORDS

Airway: obstruction. Complications: emphysema.

CASE REPORT

A healthy 37-yr-old women presented for a right stapedectomy. She had previously undergone anaesthesia and surgery uneventfully on several occasions. On preoperative assessment there were no findings of note, and the patient was categorized as ASA I.

After premedication with diazepam 10 mg, a vein was cannulated. Pulse oximetry, ECG and arterial pressure monitoring were commenced and anaesthesia was induced with propofol 150 mg, fentanyl 100 µg and atracurium 30 mg. The lungs were ventilated easily via a facemask. A good view of the cords was obtained, and intubation of the trachea was performed easily.

Anaesthesia was maintained by intermittent positive pressure ventilation (IPPV) using 66% nitrous oxide in oxygen supplemented with 1% isoflurane. Airway pressures and end-tidal carbon dioxide concentrations were measured. Right stapedectomy was performed without incident. The lung inflation pressures remained < 15 mm Hg throughout and there were no episodes of coughing or straining. After antagonism of the residual neuromuscular block with neostigmine 2.5 mg and glycopyrronium 0.5 mg, pharyngeal suction was performed blindly to clear secretions before extubation of the trachea. After a short period in the recovery area, the patient was returned to the ward.

Six hours later, the patient complained of pain and swelling in the left of her face, and of "coughing up blood". The pain and swelling became more severe each time she coughed. Her symptoms progressed rapidly over the next 1 h, by which time she was unable to open her eyes. Each cough was followed by several seconds during which inspiration was impossible, although expiration remained easy.

On examination there was surgical emphysema of the head and neck, tracking to the mid-chest. Eye opening was not possible and jaw opening was limited. There was no cardiorespiratory embarrassment. Auscultation of the chest was difficult because of soft tissue crepitus. The lung fields sounded clear and the heart sounds were normal. A chest radiograph showed a pneumopericardium, but no pneumothorax.

Because of the haemoptysis, intermittent airway obstruction and rapid progression of the condition, it was decided to transfer the patient to the operating theatre to secure the airway. Full monitoring was commenced and anaesthesia induced using halothane in oxygen, supplemented with small i.v. increments of propofol. It became possible to open the mouth and perform gentle laryngoscopy. This revealed blood in the posterior pharynx, and a pharyngeal wall and tonsillar bed tensely inflated with air and prolapsing over the glottic aperture. The pharyngeal wall was pushed posteriorly and deflated partly, using the blade of the laryngoscope. A good view of the vocal cords was obtained and tracheal intubation achieved readily.

Anaesthesia was deepened using halothane in oxygen while spontaneous ventilation was maintained. When the depth of anaesthesia was judged sufficient, the tracheal tube was removed and bronchoscopy performed. The trachea and bronchial tree appeared normal, with no blood soiling. The tracheal tube was replaced, and a pharyngo–oesophagoscopy was performed. This revealed a small, bloody perforation in the posterior pharyngeal wall just behind the arytenoids. A nasogastric feeding tube was passed, and the patient was transferred to the intensive care unit. Prophylactic antibiotics were commenced.

Over the next 24 h the surgical emphysema resolved largely and extubation of the trachea was possible. Nasogastric aspiration was continued for several days because of the risk of pharyngo-mediastinitis. Recovery was otherwise uneventful.

DISCUSSION

We have described a case of surgical emphysema occurring as a complication of an apparently uneventful anaesthetic for an extra-oral ENT pro-

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cedure. The case is interesting both because of the presumed aetiology and because of the sequence of events.

Our patient presented with cervicofacial emphysema progressing fairly rapidly to airway obstruction. This is unusual, as the condition is usually self-limiting [1], and posed problems for the management of our patient. Clearly, it was necessary to secure the airway. Initially, a tracheobronchial lesion could not be excluded; the presence of such a lesion would have contraindicated IPPV [2]. It could have necessitated the use of a double-lumen tube as for a bronchopleural fistula and the siting of a chest drain. This seemed inappropriate in the absence of a radiologically apparent pneumothorax.

Because of the patient's distressed state, an awake fibreoptic intubation was deemed impractical. Therefore, a technique using inhalation induction with spontaneous ventilation throughout was selected. Nitrous oxide was avoided because of the risk of diffusion into gas filled cavities, including the pericardium, which could have caused circulatory embarrassment [3].

Subcutaneous emphysema occurs most commonly as a consequence of pneumothorax or pneumomediastinum. It may arise also as a result of several pathologies not involving the lung. Infection with gas-forming organisms, oropharyngeal trauma [1], dental procedures (particularly those involving the use of high pressure air drills) [4–6], drug abuse [7] and even urinary catheterization [8] have been described as causes. The condition is usually self-limiting but, if mediastinitis ensues, the condition carries a mortality of up to 50% [1]. Subcutaneous emphysema must therefore be diagnosed correctly and treated promptly.

The cause of the emphysema in our patient was not immediately clear. In most of the cases quoted above, a source of compressed gas or surgical instrumentation was implicated. It seems unlikely that the problem was related to the operative field in our patient. As the most notable site of surgical emphysema—the posterior oropharynx—had sustained a small perforating injury, an anaesthetic cause was sought. The laryngoscopy at the initial operation was straightforward, and the tracheal tube was passed easily and without the use of force. It is improbable that the trauma occurred at this stage. In our hospital, pharyngeal suction is performed at the end of procedures, using plastic disposable "Yankauer" type suckers. These do not have a rose or guard shielding the tip. With the suction unit set on "full", the system delivers a negative pressure of 60 kPa. It is likely that this is sufficient to perform a mucosal suction biopsy: Brandborg, Rubin and Quinton described a technique for mucosal suction biopsy using a negative pressure of 91 kPa [9] and Noblett has demonstrated that pressures of 68 kPa are effective [10]. We have often noted the ease with which pharyngeal mucosa may be caught by the tip of a Yankauer sucker. It is therefore proposed that this was the mechanism by which the injury occurred.

The lesion behaved as a flap-valve, so that air was gradually trapped in the subcutaneous tissues. This was most pronounced on coughing or sneezing, which forced air into the posterior pharyngeal wall, causing it to balloon forward and occlude the glottis. This process was limited by the subsequent decompression of the pharyngeal wall as the trapped air spread to adjacent tissues.

We have described a case of several potentially life-threatening problems (airway obstruction, subcutaneous emphysema, pneumopericardium, risk of mediastinitis) occurring in an otherwise healthy patient as the result of an "uneventful" anaesthetic. We advise great care in the use of suction units with unguarded tips. The suction pressure should be limited to a value considerably less than that at which mucosal biopsy has been shown to occur. Minor and apparently innocent pharyngeal injuries should be clearly documented and care taken to recognize complications early.

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British Journal of Anaesthesia 1993; 71: 594–596

EQUIPMENT

RESISTANCE TO CONSTANT AIR FLOW IMPOSED BY THE STANDARD LARYNGEAL MASK, THE REINFORCED LARYNGEAL MASK AND RAE TRACHEAL TUBES

A. AL-HASANI

SUMMARY

The reinforced laryngeal mask airway (RLMA) has been introduced recently for head and neck surgery. Its resistance to constant air flow has been measured and compared with that of the standard laryngeal mask airway (LMA). The RLMA resistance has also been compared with that imposed by the standard oral Ring–Adair–Elwyn (RAE) tube of a corresponding size for a given patient. The resistance to gas flow of the new RLMA was approximately three to five times that of the LMA at two flow rates (0.5 and 1.0 litre s^{-1}*). The resistance of the RLMA 4 was intermediate between that of RAE tubes sizes 8 and 9 mm, and that of RLMA 2 intermediate between that of RAE tubes sizes 5 and 6 mm.* (Br. J. Anaesth. 1993; **71**: 594–596)

KEY WORDS

Equipment: laryngeal mask airway, reinforced laryngeal mask. Airway: resistance.

The new, wired reinforced laryngeal mask airway (RLMA) (Intavent), was introduced in sizes 2, 2.5, 3 and 4 and has been used for head, neck and dental surgery [1]. Others have used the RLMA for nasal surgery [2]. Advantages claimed by the manufacturer for the RLMA include flexibility which enables it to be bent out of the surgical field without occluding the lumen and without loss of the cuff seal against the larynx. The external diameter of the tube component has been decreased in comparison with the standard LMA in order to facilitate surgical access [1]; as a result, the internal diameter is also smaller than that of the standard LMA (table I).

The resistance to air flow imposed by tubes and airways in spontaneously breathing patients should be small, otherwise there is an increase in the work of breathing, with a concomitant increase in intrathoracic pressure and venous pressure, and increased bleeding tendency.

The narrower lumen of the RLMA would be expected to increase flow resistance compared with the standard LMA. The aim of this study was therefore to determine the resistance to constant air flow for both RLMA and LMA.

The resistance of the LMA has been compared favourably with that of corresponding sizes of tracheal tube [3]. Therefore, in the second part of this study the resistance of the RLMA has been compared with that of corresponding sizes of oral RAE tracheal tubes.

METHODS

Flow resistance was studied using dry air at room temperature. RLMA and LMA sizes 2 and 4 were used, as these represent the extremes of the size range. The laryngeal mask size 2 was compared with RAE tubes sizes 5 and 6 (21.5 cm and 24.5 cm in length, respectively), and the laryngeal mask size 4 with RAE tubes sizes 7, 8 and 9 (29.5 cm, 31.5 cm and 34.5 cm in length, respectively). These groupings were made according to the manufacturers' recommendations for patient sizes for LMA.

The measurement system was similar to that used by Bhatt and colleagues [3] (fig. 1). A tracheal model made from a plastic hose of length 10 cm and internal diameter 22 mm either was interfaced with the patient end of the LMA or received the RAE tube, passed into its lumen to simulate a tracheal intubation.

Air flow was measured using a Harvard dry gas meter, which was calibrated against the manufacturer's Harvard dry gas meter.

A constant flow of dry air was delivered from a cylinder (through a variable orifice flowmeter) and allowed to pass through the gas meter, where the volume delivered over 3 min was determined; from this, the volume over 1 min was calculated to give a flow rate in litre min^{-1}. The air then passed through the LMA or RAE tube. Pressure difference was measured between two points—one in the centre of the proximal connector of the tube and the other in the centre of the tracheal model 1 cm distal to either the vertical bars of the cuff or the bevelled end of the RAE tracheal tube.

Pressure measurements were made using a silicon piezo-resistive strain gauge transducer (No. MPX10DP, Motorola incorporated) coupled with a voltmeter to give a digital display. This was calibrated using a water manometer and found to be linear in the range 0–40 cm H_2O.

A series of different flow rates (in the range 0–60 litre min^{-1}) were studied and corresponding pressure differences measured. These data were

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TABLE I. *Internal diameters and lengths of different size RLMA and LMA*

	LMA 2	RLMA 2	LMA 2.5	RLMA 2.5	LMA 3	RLMA 3	LMA 4	RLMA 4
I.d. (mm)	7.0	5.1	8.4	6.1	10.0	7.6	10.0	7.6
Length (mm)	120	130	135	165	175	210	175	210

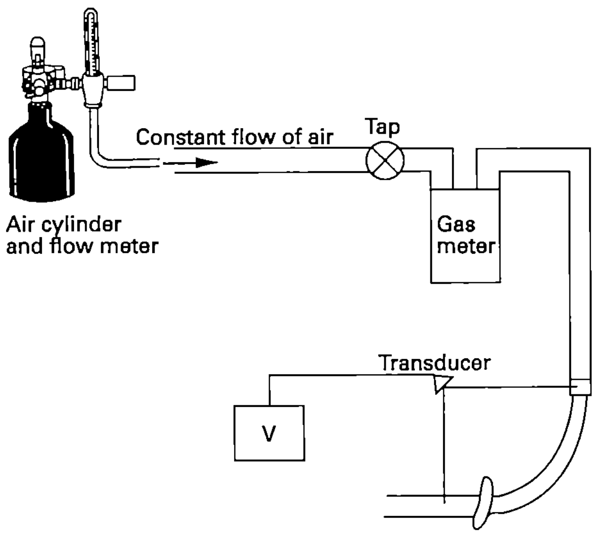

FIG. 1. The system of measurement.

plotted and the line of best fit obtained using a Sigmaplot computer program.

RESULTS

Pressure–flow relationships for the RLMA, LMA and RAE tubes are shown in figure 2. To determine flow resistance, the sigmaplot program was used to solve the polynomial equation describing each curve. By substituting two standard flow rates (0.5, 1.0 litre s^{-1}) in the equation, the corresponding pressure gradients were calculated.

Resistance was thus calculated as R = Pressure/Flow at 0.5 and 1.0 litre^{-1}, expressed as kPa litre^{-1} s. The resistance of the RLMA to constant air flow, was approximately three to five times that of the LMA at these two standard flow rates (table II).

The resistance of the RLMA 4 was intermediate between that of RAE tube sizes 8 and 9 and that of the RLMA 2 was intermediate between that of RAE tubes 5 and 6.

DISCUSSION

Measurement of flow resistance in a tube depends upon the location of the points at which differential pressure is measured, and on the disposition of the transducer (perpendicular, opposite to, or in the direction of air flow). In this study, the catheter tip of the transducer was perpendicular to the direction of the flow. Measurement of air volume in this study was performed over 3 min in order to reduce any error in volume measurement per unit of time.

For each tube, at a certain flow rate there was some fluctuation in the differential pressure measurement because of turbulent flow. When this occurred, the pressure difference taken was the average of the values at that flow rate.

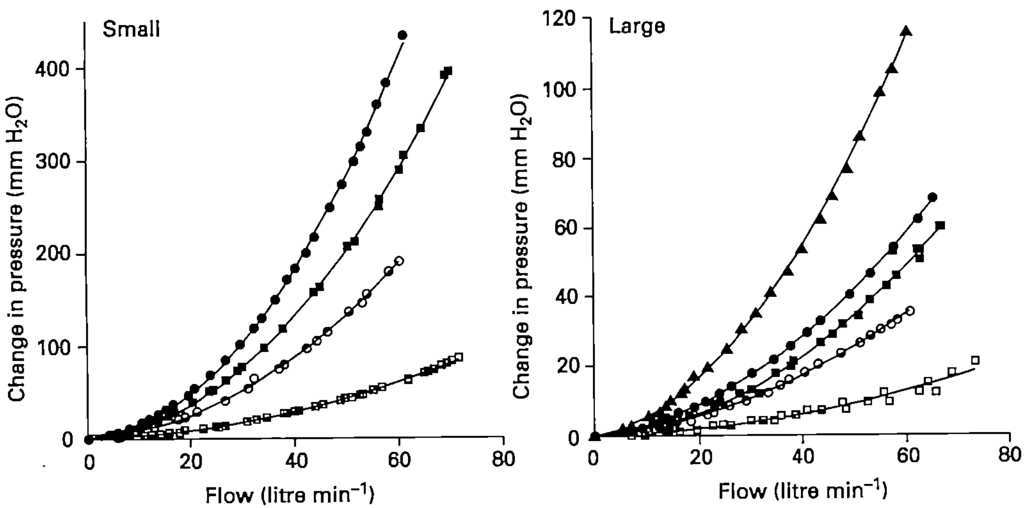

FIG. 2. Pressure–flow relationships for small and large RLMA, LMA and RAE tubes. Small tubes: □ = Standard LMA size 2; ■ = reinforced LMA size 2; ○ = RAE size 6; ● = RAE size 5. Large tubes: □ = Standard LMA size 4; ■ = reinforced LMA size 4; ○ = RAE size 9; ● = RAE size 8; ▲ = RAE size 7.

TABLE II. *Resistance at flow rates of 0.5 and 1.0 litre s^{-1}, for all sizes of LMA, RLMA and RAE tubes studied*

Flow rate (litre s^{-1})	Resistance (kPa litre^{-1} s)								
	LMA 2	RLMA 2	RAE 5	RAE 6	LMA 4	RLMA 4	RAE 7	RAE 8	RAE 9
0.5	0.285	1.346	1.842	0.913	0.064	0.236	0.583	0.308	0.189
1.0	0.522	2.555	3.596	1.671	0.112	0.436	1.01	0.516	0.311

The constant flow rates of air used in this study are similar to those used by other investigators to determine the resistance of tubes [3, 4], but obviously this does not simulate the moment-to-moment change in flow rate during the ventilatory cycle, with possible turbulent flows during different stages of the cycle. Thus these measurements tend to underestimate the flow resistance.

As may be expected, the resistance offered by the new RLMA was found to be greater than that of the LMA. Bhatt and colleagues [3] found that the additional inspiratory work of breathing was proportional to the resistance imposed by the tracheal tube or LMA. It may be expected, therefore, that the RLMA, with a greater resistance than that of the LMA, would cause a greater increase in the work of breathing than that imposed by the LMA. In the present study, there were no advantages for the RLMA compared with RAE tubes in respect of flow resistance and, therefore, work of breathing.

Further work is needed to quantify the load added to the work of breathing of each type of tube in a clinical setting. In this situation, other factors may have a role, for example the amount of gas flow around a non-cuffed tube or the change in calibre of the anatomical airway in response to the presence of LMA.

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COMMENTARIES

EFFICACY OF THERAPEUTIC SUGGESTIONS PRESENTED DURING ANAESTHESIA: RE-ANALYSIS OF CONFLICTING RESULTS

K. MILLAR

SUMMARY

Re-analysis has been made of two clinical studies which used similar methodologies but found different effects of so-called therapeutic suggestions presented to anaesthetized patients undergoing abdominal hysterectomy. The re-analysis suggested that when data from the two studies were examined jointly, it was uncertain if positive suggestions had a reliable influence upon the recovery measure of "days to discharge". The supposed positive effect reported in one of the studies may arise from a rather different distribution of data in the control group. It is proposed that the effect may be attributable to chance bias in allocation of patients to the control group, or to some other chance anomaly in the composition of the group as a result of relatively small sample size. The importance of sample size is discussed in relation to detection of effects when only a few patients may be in a state susceptible to intra-anaesthetic suggestions. The importance of presenting data distributions in addition to summary statistics is also emphasized. (Br. J. Anaesth. 1993; **71**: 597–601)

KEY WORDS
Anaesthesia: depth. Memory.

The possibility that apparently adequately anaesthetized patients might be capable of establishing unconscious or "implicit" memories for auditory information presented during surgery has attracted much research interest and theoretical speculation [1, 2]. One aspect of the supposed phenomenon that would have important clinical applications is the proposal that therapeutic suggestions presented during anaesthesia might have beneficial effects on postoperative recovery. As Block and colleagues [3] have pointed out, if such suggestions were effective, they would not only enhance the subjective wellbeing of the patient, but also reduce the cost of hospital treatment by decreasing the time to discharge.

Equally, however, when reviewing the highly discrepant findings on the phenomenon in the research literature, the same authors concluded that "it remains almost miraculous that suggestions can be helpful when administered to an unconscious patient." The pattern of published results may be relevant to their conclusion, because it indicates that there is no consistent evidence that positive suggestions are effective: of eight recent studies published in peer-reviewed journals, three have shown positive effects [4–6] whilst five have shown negative effects [3, 7–10]. It is difficult to determine the basis of such inconsistent results because the studies have, with two exceptions considered in detail below, used different methodologies which therefore confound potentially salient variables.

Moreover, the published reports have, with three exceptions, presented their outcome data in the summary form of means and SD. Such data presentation may be misleading for two contrasting reasons. First, a statistically "significant" difference between two groups of patients in, say, the time to discharge after surgery, may be caused by large differences in only a few of the patients in one of the groups [11]. The duration of stay in those few individuals may be sufficiently long, or short, to produce an overall "significant" difference between the means. The opportunity for a few individuals to distort "true" treatment effects is, of course, increased when a study involves only small sample sizes. However, had the data distributions of the two groups been examined, they would probably be found to have very considerable overlap indicating that, in both groups, the range of time to discharge was similar. While such an effect is of interest because it illustrates the importance of individual variation, this is rarely the conclusion drawn by researchers, nor indeed by those who cite the research. On the contrary, rather than report that the means are different because only a few patients are (apparently) affected by the treatment, the conclusion tends to be that the mean effect indicates a *general* difference between the two groups; that is, that *all* patients in one group are significantly affected by the treatment.

By the same token, where two means do *not* differ significantly, this may mask the presence of some individuals who are, relative to their fellows, much affected by the treatment [11]. Again, the debatable general conclusion may be drawn that there is no reliable difference between the treatments involved.

Gardner and Altman [12] and Matthews and colleagues [13] have argued that better insights to

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This article is accompanied by Editorial II.

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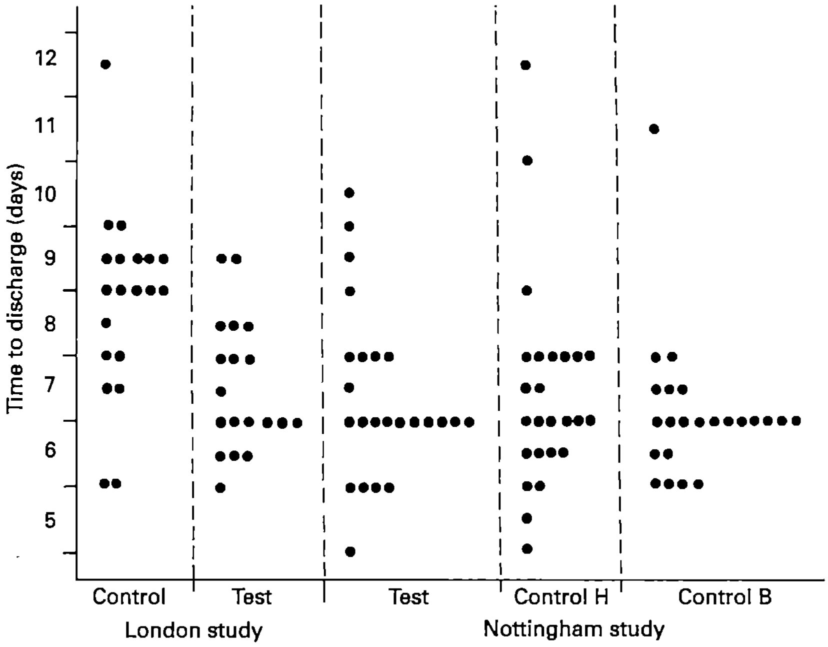

FIG 1. Distribution of individual patient data points (days to discharge) in the two groups of Evans and Richardson in London [5] and three groups of Liu, Standen and Aitkenhead in Nottingham [9]. "Suggestion" groups (test) were presented with therapeutic suggestions during anaesthesia. The suffixes "B" and "H" indicate that those control groups received a blank or "history" tape respectively, in the Nottingham study (see text).

treatment effects may be gained by presentation of full data sets in graphical form. Such an approach gives a very clear impression of the range of effects associated with different treatments and also allows identification of individuals whose response may differ markedly from the rest of the sample. Such an approach would seem invaluable in the present area of research, in which there is considerable uncertainty concerning the true nature of the effect (if any) of therapeutic suggestions. It takes account of the hypothesis that only a few individuals may be susceptible to the influence of suggestions, possibly as a result of inadvertent states of relatively light anaesthesia. This point is discussed below in greater detail.

The studies of therapeutic suggestions by Bonke and colleagues [4], Evans and Richardson [5] and Liu, Standen and Aitkenhead [9] are valuable because they have presented the individual data for each patient and therefore permit examination of the data distributions. Furthermore, as the study by Liu's group aimed to replicate the earlier study of Evans and Richardson, the two methodologies are sufficiently similar to permit direct comparison between the results.

Re-analysis

Evans and Richardson [5] reported a significant effect of therapeutic suggestions in their study conducted in London (hereafter "the London study"): their study group left hospital on average 1.3 days before the control group. However, Liu, Standen and Aitkenhead [9] did not replicate this finding in their study conducted in Nottingham (hereafter "the Nottingham study"). It is within the scope of the present paper only to give brief details of the methodologies used in the two studies and the reader should refer to the original publications.

The London study involved two groups of women undergoing total abdominal hysterectomy. The suggestion group ($n = 19$) was presented with recorded suggestions for faster recovery, fewer postoperative problems and enhanced feelings of wellbeing during the recovery period. A control group received a blank tape ($n = 20$). The published report did not describe the anaesthetic procedure, but access to unpublished details of the study has revealed that induction was with thiopentone, followed by enflurane and fentanyl in some 85 % of patients, while unspecified "other" agents were administered to the remainder.

The Nottingham study of patients undergoing total abdominal hysterectomy was designed as a replication of the London study, but with an added control group. The experimental group ($n = 24$) received recorded suggestions identical to those used by Evans and Richardson, the "history" control group ($n = 25$) received a recorded history of the hospital in which the patients were being treated in order to control for any simple beneficial effects of a voice during surgery, and the control group ($n = 24$) heard nothing. The procedure involved premedication with papaveretum and prochlorperazine, and anaesthesia with thiopentone and vecuronium, and nitrous oxide and enflurane in oxygen.

In the original publications, the data distributions were presented as stepped functions to show the number of patients still in hospital over time. While this representation is superior to that of simple reporting of mean and SD, it is less informative than the routine advocated above [12, 13]. Therefore, data from the two studies have been re-graphed and are shown in figure 1.

With this presentation, it becomes evident that, while four of the groups were similar in their mean and range duration of stay in hospital, the London

TABLE I. *Upper panel: Mean* (SD) *days to discharge of patients in the studies by Evans and Richardson (London) (LC and LS groups) and Liu, Standen and Aitkenhead (Nottingham) (NS, NC–B and NC–H groups). "Suggestion" groups received tapes of therapeutic suggestions during anaesthesia. Suffixes "B" and "H" denote the control groups receiving a blank or "history" tape, respectively, in the Nottingham study (see text). Middle panel: The highly significant ANOVA indicates that one or more of the groups differed from each other. Lower panel: Comparison of means shows that the LC group differed significantly from all other groups. Further comparisons (not shown here) indicate that the other groups did not differ from each other. The criterion for statistical significance was set at* P = *0.005 to cater for an increased risk of Type-1 error arising from multiple comparisons (see text). SS = Sum of squares; MS = mean square*

Group	*n*	Mean (SD) time to discharge (days)
London control (LC)	20	8.4 (1.44)
London suggestion (LS)	19	7.1 (1.01)
Nottingham control (NC–B)	24	6.6 (1.09)
Nottingham control (NC–H)	25	6.9 (1.60)
Nottingham suggestion (NS)	24	6.9 (1.31)

ANOVA

	SS	df	MS	*F*	*P*
Between groups	37.01	4	9.25	5.31	0.0006
Within groups	186.36	107	1.74		

Comparison of means (LC *vs*:)

	LS	NS	NC–H	NC–B
P	$t_{37} = 3.17$ < 0.004	$t_{42} = 3.43$ < 0.003	$t_{43} = 3.02$ < 0.005	$t_{42} = 4.45$ < 0.001

control group had an average longer duration of stay and the general distribution favoured longer periods in hospital before discharge. One-way analysis of variance confirmed a highly significant main effect of groups ($F_{4,107} = 5.31$, $P = 0.0006$), indicating that one or more of the groups differed reliably from the other (table I). *Post hoc t* tests conducted with pooled variance estimates confirmed that it was the London control group which differed from all the other groups, none of which differed from the others (table I). The Bonferroni correction was applied to the multiple comparisons to cater for the increased risk of Type-1 error. The conventional alpha level of 0.05 was divided by the number of comparisons (12) to give an appropriate criterion for significance of $P = 0.005$.

Conclusions on the re-analysis

These results permit several different conclusions. If the effect of suggestions upon London patients is reliable, it would seem only to result in reducing the recovery period to that normally attained in Nottingham regardless of positive suggestions. This might be explained by the proposal that the London patients were generally less well and that the suggestions were effective in reducing the duration of their stay which, for reasons of their poorer health, would otherwise have been protracted. Bonke and colleagues made a similar proposal to explain age-related effects of positive suggestions by which only elderly patients were seen to benefit from the suggestions [4]. While this is plausible, Bonke and his colleagues have not subsequently replicated the effect [8]. One might also propose that the London and Nottingham samples differed because of other patient-related factors, but examination of potential confounding variables which are shown in the data tables of the original papers indicates that the groups did not differ on these measures.

A further possibility is that the two hospitals differed in their discharge criteria. If such criteria were applied more stringently in Nottingham, so that patients tended to be discharged after a fixed period in hospital, this might mask any beneficial effect resulting from therapeutic suggestions. Figure 1 indicates that all Nottingham groups had a preponderance for discharge to occur after 6.5 days (7.5 days for control group H). This might seem to imply a relatively fixed discharge period applying to the Nottingham patients, but figure 1 also shows a similar preponderance for patients to be discharged at 6.5 days in the London suggestion group. This might imply that, if discharge criteria are somewhat rigid, it is true of both hospitals. Thus the significantly longer period spent in hospital by the London control group continues to appear anomalous: within that group, most patients tended to be discharged after 8.5 or 9 days.

One might be cautious, therefore, in assuming that "positive suggestions" influence discharge periods in the London study, but deduce rather that there is something "different" about the London control group. A relevant consideration lies in the factor of individual variation between patients. The first example of this lies in inadvertent bias in the allocation of patients to groups. Even when allocation to treatment conditions is randomized, there is the chance that patients sharing particular characteristics which may predispose them to longer hospital stay are allocated in disproportionate numbers to a particular treatment condition. As noted above, the risk of such bias giving rise to misleading treatment effects may be high when relatively small sample sizes are involved, as in the case of the London study.

In this respect, one might note that the Nottingham study was of about 25% larger samples. Examination of their distributions in figure 1 shows the presence of some patients who experienced considerably longer stays than the others. The wider range in scores is an expected consequence of increasing the sample size which, in turn, makes that sample more representative and more reliable. With a larger sample, there is less opportunity for a few extreme scores to bias the mean result; but with small samples this remains a possibility.

The theme of individual variation is also relevant to the possibility of detecting the influence of intra-anaesthetic suggestions, assuming that such suggestions have the potential to be effective. It is acknowledged that there is variation between patients in their state of anaesthesia: such states may be critical to the potential for therapeutic suggestions to exert an effect. Empirical evidence indicates that few patients have conscious recall of intra-anaesthetic events, but a greater proportion (still small in absolute terms) may be in an amnesic–analgesic state in which they experience, and report subsequently, dreams or other indistinct perceptions which might be related to the anaesthetic period [14–16]. In such a state, patients *may* be susceptible to the registration of auditory information, although it is another matter if it might influence their subsequent behaviour. One assumes the amnesic–analgesic state corresponds to a state of relatively light anaesthesia.

Given that relatively few patients are likely to be in such a state, the chance that a small patient sample may include such patients is, in turn, small. Even if a sample of 20 patients should include two or three who might be susceptible to, and influenced by, auditory information, the chance of detecting the effect by conventional analysis of mean group differences may be slight. Analysis of individual patient data as in figure 1 might provide more insight, but even if the scores of one or two patients should lie in a direction which appeared to favour the hypothesis of benefit from intraoperative suggestions, it might be difficult to ascribe the "effect" to anything other than random variation.

Sample size would seem to be important, therefore. In both the London and the Nottingham studies, samples comprised between 19 and 25 patients. From the argument above, one has to consider carefully if a reliable effect of therapeutic suggestions might be shown with such samples.

Therapeutic suggestions are one example of methods used to measure what is termed "implicit" or unconscious memory. When auditory information has been retained from an intra-anaesthetic episode, the patient may reveal the memory by unconscious changes in physical or verbal behaviour. As in the specific case of therapeutic suggestions, there is variable evidence on the reliability of implicit memory effects in general. Given the discussion above, this may again support the proposal that only a few patients are in a potentially "receptive" anaesthetic state. Indeed, Block and colleagues [17] explicitly noted that their demonstration of implicit memory effects on a word completion test was evident in only a relatively small proportion of the sample. However, the implicit effect did not appear to vary as a function of end-expired concentrations of anaesthetic (1.0–1.5 MAC isoflurane), a result which runs counter to the argument above on the potential importance of the anaesthetic state.

There is, however, little doubt as to the importance of attempting to define the anaesthetic state in studies of implicit memory: Winograd and colleagues [18] have pointed to the difficulty in evaluating positive or negative results in the absence of information on the probable state or depth of anaesthesia. Studies of the auditory evoked response during anaesthesia would seem to offer great promise in this area, particularly when electrophysiological data concerning the anaesthetic state can be related to subsequent implicit memory for verbal material presented during the anaesthetic [19].

In conclusion, when a direct comparison is made between the studies of Evans and Richardson [5] and Liu, Standen and Aitkenhead [9], it may be uncertain if therapeutic suggestions were responsible for the between-group differences in the discharge periods in the London study. Comparison of the data distributions reveals marked similarity between all but one of the groups concerned, suggesting that the London control group was in some way aberrant. By chance, this may have led to a difference between means which happened to be consistent with the hypothesis favouring a benefit deriving from therapeutic suggestions.

Reference to figure 1 confirms the considerable variation between patients in the time to discharge. If therapeutic suggestions do have a reliable effect then, for that effect to be revealed, it must be of a magnitude sufficient to exceed the random variation which occurs naturally between patients. Considerably larger sample sizes are required to obviate misleading biases caused by chance allocation of particular patients to treatment conditions, and to account for the possibility that only a few patients in a given sample may be in a state to register intra-anaesthetic auditory information. It would also seem important to define objectively the anaesthetic state at the time of input of verbal information, in order to determine if there is any correlation between that state and the probability of subsequent implicit or explicit retrieval of the material.

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WHY DO ANAESTHETISTS NEED CODES?

R. M. TACKLEY, M. E. STUART-TAYLOR AND M. HURRELL

SUMMARY

With the increasing availability of information technology in hospitals and the introduction of medical audit and resource management, there is a proliferation of anaesthetic data collection systems. The amount of data recorded varies from a complete anaesthetic record to a small subset of it. Most systems hold data in coded form for reasons of accuracy and compactness. Unfortunately, all the coding systems are different, making comparisons between different centres difficult. We propose that there is a need to develop a standard national system for coding anaesthetic terms (Br. J. Anaesth. 1993; **71**: 602–606)

KEY WORDS

Anaesthesia: coding of terms, standardization, nomenclature.

As a combined result of the U.K. government's new requirement for hospital information systems and the rapid increase in power of affordable computers, there is a wealth of clinical data being collected. This is likely to increase rather than decrease, with sections (eventually all) of patient's records being stored and transferred electronically. Anaesthetic records are already being generated and stored electronically [1–3], but to date there has been no universally agreed format in which such complex information may be manipulated. This has resulted in the frustrating and limited application of computerized data [4].

The aim of this paper is to present the need for a common vocabulary of terms in the practice of anaesthesia, particularly when computerized record systems are used, and consider how this may fit into medicine as a whole.

DISCUSSION

Anaesthetic records can be stored electronically in several formats. Each anaesthetic sheet may be held as a picture derived in the same way as images by a fax machine. This implies that the whole record may be stored, retrieved or transferred electronically. However, it would be extremely difficult to search for specific information about that patient's anaesthetic without reading the whole record, because the written word would be stored as a "picture". It is possible to allow powerful computers to "read" these pictures and thus look for specific items, such as the term "crash induction", but this is expensive and inefficient. Whilst this might be feasible with a small number of records, it is clearly impractical with, for example, the entire output from one anaesthetic department. If one extends this concept to searching data from an entire nation, then such a concept is impossible.

Is it necessary to store anaesthetic information electronically?

This is answered best by examining the functions of recorded information.

First, there is a growing need for anaesthetic departments to collect information on anaesthetic and theatre activity in hospitals [5]. For example, it is useful for monitoring trainee supervision and experience, case-mix, throughput times, individual workload, out-of-hours work load, and so on [6]. If accurate and meaningful data can be collected, the information derived may be used for audit and resource management.

Second, health regions, the Royal College of Anaesthetists and, ultimately, the Department of Health require distillates of information collected at departmental level. Such items would include trainee supervision and experience, and critical incidents. Discussion is currently under way with the Royal College to establish common minimum data sets for use throughout Great Britain. However, the entire system breaks down at the first stage—that is, trying to compare data from different hospital systems if they are using different definitions and different coding systems.

Finally, there is a requirement to describe anaesthetic events in more accurate and comprehensive ways. Until recently, this was done entirely using pen and paper with, in particular, differing amounts of data collected on vital signs. These variables are represented with a variable degree of accuracy—how many of us have smoothed out a low arterial pressure reading in the anticipation that it was certain to recover with the next recording [7]? How many records have insufficient or illegible data recorded on them? This is especially highlighted when one attempts an audit by searching through case notes.

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Not only does this lack of data restrict information available for subsequent anaesthetics, but it also has serious legal implications in the unfortunate circumstance of a litigious enquiry [8]. Absent information is interpreted in the Court of Law as absence of appropriate activity and may contribute to losing the case [9]. Some of these problems can be overcome by automated entry of data and there are already several automated anaesthetic record-keeping systems available commercially [1, 2].

How do we best represent data in a computer-compatible form?

The human mind is capable of reading different terms or phrases such as "top circuit" or "Magill breathing system" and interpreting them as meaning one and the same thing. A computer cannot unless it has been specifically instructed that they are synonymous. A computer, however, has enormous power to collate, integrate, sort, query and compute in a way that the human brain cannot. We have, therefore reached a stage where the human brain must apply itself to recording information in a way that can be exploited easily by computer. We must decide not only which terms to put into the computer, but also which terms imply the same meaning. For example, do "top circuit" and "Magill breathing system" and "non-coaxial Mapleson A" mean the same? If they do (and it is not the remit of this paper to address this question), the next task is to decide which phrase is most likely to be used and understood by health care personnel. If we are able to produce one commonly used phrase or rubric, the preferred term, and instruct the computer to record that rubric whenever any of the predetermined acceptable alternatives is entered, we are taking the first step towards defining a common medical language.

Abbreviations and acronyms

As an extension of this concept, the medical profession relies heavily on the use of abbreviated terms. For example 16G (iv) D R H, Thio, Sux, GO(35%)E, #8 COTT, IPPV...etc. If the computer can be instructed to interpret these abbreviated synonyms and not to confuse them with similar abbreviations in a different context, for example B.S. (bowel sounds or breath sounds), then we are approaching a situation in which the person entering the data has the freedom to choose his own preferred synonym or shorthand.

Why store information as codes?

The next step in the process of computerizing information is to assign a unique code to the unique preferred terms. The advantages of storing information as codes may be considered under the headings of human factors and computer-related factors. For this discussion, a code will be taken to refer to a short, unique sequence of alphanumeric characters.

Human factors. (1) Codes are able to express an item of information unambiguously by representing a unique preferred term. Synonymous medical language terms can be mapped onto a code with a unique meaning. For example: "heart attack" = "myocardial infarction" = "coronary thrombosis" = UNIQUE CODE.

(2) The use of codes encourages consistency in definitions. For example, a code for a drug should be able to provide the unique label for that drug in a particular formulation. Another example is "emergency operation", which may imply simply "non-elective" or may reflect the strict CEPOD definition of "immediate operation, resuscitation simultaneous with surgical treatment—operation usually within one hour". In this case there would be a need for two unique codes to provide labels for the concepts.

(3) It ensures that all people understand exactly what is being expressed. A code is a point of convergence between several medical language terms, but these themselves may be in several different languages. This confers a great advantage when patients are transferred within Europe or internationally, and possibly when information about international medical issues is being gathered.

Computer-related factors. Here, the advantages of coding are related to the inefficiency and problems of computerized handling of "text strings". These may be defined as phrases made up of any combination of characters, numbers, spaces or punctuation. The main problems are as follows:

(1) Text strings are often imprecise and unpredictable in content, because they are usually entered by people. For example: "intermittent positive pressure ventilation" = "continuous mandatory ventilation" = "artificial ventilation". Also, in such long text strings there is a big risk of mis-spellings, unrecognized abbreviations, etc.

(2) Text strings usually take up more storage space than codes and this is still expensive to provide. For example, a Read code is five alphanumeric characters long, but it provides a unique label for a term up to 198 characters long—a saving of nearly 40 times. This is again compounded by the fact that, in most code databases, the terms have to be repeated many times in mapping tables.

(3) Text strings take longer to search for all types of data, especially precision numerical values and this slows down the programs using the codes by another large factor.

(4) Codes may have a fixed length, which makes for faster computation. Even with only five alphanumeric characters, more than 600 million unique codes are possible.

How would the codes be used?

It must be stressed at this point that the actual code allocated to each term in a classification system should be invisible to the user, as all that is required is an accurate and easy method of selecting the correct term. The software of the computerized system using the codes should then be capable of assigning the correct code to each term entered and this must be made invisible to the user.

Which coding system?

The attributes for an ideal medical terminology system have been noted elsewhere [10]. The main

TABLE I. *Classification of anaesthetic type at Torbay Hospital*

0	No anaesthetic given
1	Sedation only
2	General anaesthetic with spontaneous ventilation
3	General anaesthetic with spontaneous ventilation and tracheal intubation
4	General anaesthetic with intermittent positive pressure ventilation
5	General anaesthetic with intermittent positive pressure ventilation and tracheal intubation
6	Total i.v. anaesthetic with spontaneous ventilation
7	Total i.v. anaesthetic with spontaneous ventilation and tracheal intubation
8	Total i.v. anaesthetic with intermittent positive pressure ventilation
9	Total i.v. anaesthetic with intermittent positive pressure ventilation and tracheal intubation

TABLE II. *Classification of local anaesthetic procedures at Torbay Hospital*

0	No LA procedure
1	Local anaesthetic infiltration
2	Regional local anaesthetic block
3	Extradural
4	Spinal
5	Caudal
6	Plexus block
7	Bier's block
8	Extradural already *in situ*
9	Other local anaesthetic/pain relief procedure

requirements of a national anaesthetic coding system are as follows:

(a) It should be used by all systems, to ensure compatibility.

(b) It should cover every item of medical information that may require handling by a computer such as diagnoses, operations, treatments, etc. In fact, it must be very comprehensive, otherwise it would be necessary for it to be mixed with yet another system.

(c) It should be cross-referenced to national coding systems already in use, such as OPCS4 [11], ICD-10 [12].

(d) It should be dynamic. That is to say that new terms for coding may be added as the medical language grows. Examples of these are "H.I.V." and the "laryngeal mask airway", neither of which existed as a medical term until this decade.

What existing coding systems are there for anaesthesia?

There are already many local coding systems in common use throughout the British Isles. Some of these have been described during meetings of the Society for Computing and Technology in Anaesthesia. Commonly, they include a simple set of terms to cover the majority of general anaesthetic techniques such as those listed in table I. They also usually have a short list of local anaesthetic techniques (table II). Some include codes for common critical incidents, sites of anaesthesia, drugs used, grade of anaesthetist and so on.

However, they are all different! They are not cross referenced to National coding systems and hence cannot be used for national statistics. They are not comprehensive. For instance, they do not usually include terms which would be needed for a preoperative assessment record, such as symptoms, diagnoses and illness scoring systems. They are dynamic, but only according to local changes. There appears to be none at present that fulfils the criteria put forward in the previous section.

There are very few National coding systems which address anaesthetic procedures. OPCS-4 includes a very limited number of anaesthetic procedures. CPT-4 [13] is used in the U.S.A. mainly for costing, and has only limited detail for anaesthesia and intensive care. ICD-9 contains some diagnoses that are usually made by anaesthetists, such as "Mendelson's syndrome as a complication of care". However, ICD-9 and ICD-10 are both lacking in the detail that we might need to record other complications of anaesthetic procedures, such as "pneumothorax during intermittent positive pressure ventilation".

In 1990 The Secretary of State for Health acquired the Read clinical classification (RCC) for the N.H.S. and there is currently in progress a 2-year project, named the Clinical Terms Project, organized at a national level to enhance the RCC [14, 15] so that it includes terms used in every area of medicine, including anaesthesia.

There are disadvantages of coding systems

First, one cannot guess the meaning of a code and therefore one sacrifices a degree of openness. Thus, if the text is coded incorrectly, it is almost impossible to correct it unless the original data are available. In practice, however, it should never be necessary to correct the code manually—the software should always provide translation to a term and the correct context.

Second, an endemic problem of all coding systems is that they have an inherently rigid structure and hence can never handle certain types of information satisfactorily on their own, for example continuously variable or parametric data such as "systolic arterial pressure of 127 mm Hg" or "pulmonary arterial blood pH of 7.38". The numerical value may be recorded in any amount of detail and thus require an infinite number of terms on its own! In fact, in each case, one is linking five items of data, each of which may vary independently. For example, one may wish to record diastolic pressure or pulmonary capillary wedge pressure, other numerical values and different units. If one had a code for the complete phrase given in the above example, there would be a need for a vast range of codes to express every different value for the arterial pressure. This is clearly not an efficient use of codes.

Some complex concepts need a combination of terms

The problem of forming a complex phrase can be overcome using defined rules of syntax for joining different terms. In everyday conversation, people group together terms and their interpretation and importance depend upon the context. For example, to convey the information that a patient has a "PAOP of 13 mmg Hg" assumes prior knowledge by the receiver that the patient under discussion is Mr Smith who has had a pulmonary artery flotation catheter inserted and that the pulmonary artery

TABLE III. *Example of framing for an anaesthetic event*

- Time of pre anaesthetic assessment encounter
    - ASA I
    - Premedication prescription
        - Drug
            - Dose
            - Route
        - Time prescribed for administration
    - ...
    - ...
- Pre anaesthetic assessment encounter end
- ...
- Time premedication actually administered
- ...
- Time patient arrives in anaesthetic room
- Time of anaesthetic procedure encounter start
    - Effect of premedicant noted
    - Insertion of cannula
        - 23G Y-can
        - Dorsum of left hand
    - I.v. induction
        - Agent given
        - Dose given
    - Analgesic agent
        - Dose given
    - Insertion of #3 laryngeal mask
    - Breathing system used
        - Mapleson A
    - Spontaneous ventilation
    - Maintenance of anaesthetic by inhalation agents
        - Oxygen 33 %
        - ...
    - Time patient taken into operating theatre
        - Patient position for operation
            - Left lateral
        - Time of first surgical incision
        - Vital signs monitored
        - ....
        - Critical incidents (if any)
        - ......
        - Time of wound closure
    - Reversal of anaesthesia
    - Time into recovery area
    - Vital signs
    - Time of discharge to ward
- Anaesthetic theatre encounter end

occlusion pressure has been measured as 13 millimeters of mercury greater than atmospheric pressure.

Similar information can be understood by a computer if it has a predetermined structure. This is a way of grouping codes into a certain context to give them meaning.

Table III represents some of the information concerning the activities of an anaesthetic event. The opening term marks the start of the anaesthetic preoperative assessment encounter. It is ended by a similar closing term which completes the frame of information. Within the frame there are other terms which add detail to the encounter, but are all within its context. For example, the act of "Premedication prescription". This itself may be qualified further by another frame, "Drug dose"—and so on. Each sublayer represents a finer aggregate of data of its parent frame.

The function of the framing structure is to attribute codes to particular procedures or events and thence, in a hierarchial sense, to collections of procedures and so forth. This makes up a complete anaesthetic "message".

All anaesthetic records stored electronically require a structure within which the terms are to be placed. This is usually specified by the software being used, but if we wish to communicate this information, then a standard anaesthetic record structure will be needed. At present, the Department of Health is developing these types of message structures for different topics of medical information and it is important that any anaesthetic record message structure is approved by anaesthetists.

CONCLUSION

In conclusion, there is clearly an increasing need to collate, compare and contrast data at departmental, regional and national levels in order to facilitate all aspects of anaesthetic information. It is needed for audit, to provide easy access to information about previous anaesthetics, to provide logs of trainee experience and resource management. It is likely that computerization will assist enormously in these tasks. Although this data transfer can be achieved in a standard text format, it is more efficient and accurate to transfer such information in a common coded format. This does not necessarily involve coding the entire anaesthetic record, but because technology is developing so rapidly it is logical to have the provision to be able to code *any* item of information that may be needed.

Future progress depends on a national decision to adopt one coding system for anaesthesia. This will enhance the development of national definitions of terms, anaesthetic record-keeping programs, integrated audit projects and resource management.

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CORRESPONDENCE

BJA—DANGEROUS AT LOW LEVELS

Sir,—We should like to report disadvantages to the new style (laminated) cover of *BJA*.

First, it is no longer possible to use the white band of the front cover for recording of progress, completed reading or pages/references for storing.

Second, we feel sure that we are not the only anaesthetists who have neither the space nor the time for journals at work and who receive journals at home. One colleague admits to storing journals in the garage. (Is the new cover designed to be more waterproof?) Work space at home is limited and the floor may become a useful extension; this is a potential health hazard. One of us, while rushing to answer the telephone, slipped on a recent edition of *BJA*, sustaining a wedge fracture of a lumbar vertebra, requiring partial immobilization for 3 months, cancellation of holiday and inability to work. Where this journal is concerned, anaesthetists should tread lightly.

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CONTINUOUS SUBDURAL BLOCK

Sir,—The report of continuous subdural block by Collier, Gatt and Lockley [1] raises some issues about the management of a suspected subdural block. In many instances, the diagnosis is made with certainty only in retrospect, by radiological contrast studies, and there are few guidelines to help at the time of uncertainty when the differential diagnosis between intrathecal block or multicompartment block may not be clear. In such circumstances, many would apply the "if in doubt, take it out" maxim and possibly attempt either to repeat the extradural at another space or perform a subarachnoid block. If credence is given to the postulate that large volumes of subdural local anaesthetic may cause neurological damage by compressing spinal nerve roots, blood vessels or the cord [2], repeating the extradural at an adjacent space may exacerbate such a compressive effect. As the subarachnoid contents may be displaced by subdural fluid [2], locating the subarachnoid block may be more difficult, or the height of block affected. Given appropriate monitoring, small volume continuous subdural analgesia may be applied safely, but perhaps with greater safety using single end-hole rather than multiple end-hole extradural catheters.

Unlike Dr Collier's patient, I found that prolonged postoperative analgesia was a feature with subdural fentanyl 50 μg in a case confirmed by subdural contrast [3]—the patient did not require any postoperative analgesia.

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1. Collier CB, Gatt SP, Lockley SM. A continuous subdural block. *British Journal of Anaesthesia* 1993; **70**: 462–465.
2. McMenemin IM, Sissons GRJ, Brownbridge P. Accidental subdural catherization: radiological evidence of possible mechanism for spinal cord damage. *British Journal of Anaesthesia* 1992; **69**: 417–419.
3. Rowbottom SJ, Kong AS, Chan M, Tabrizian I. Subdural block. *Anaesthesia and Intensive Care* 1993; **21**: 132–133.

Sir,—Dr Rowbottom's letter has highlighted the dilemma facing clinicians in the Labour Ward when an apparently normal extradural block develops atypical spread. The differential diagnosis between an accidental subarachnoid or subdural block or a high extradural has often to be made rapidly, on purely clinical grounds without the benefit of radiology, and a decision made as to how to proceed in the provision of Labour Ward analgesia or Caesarean section anaesthesia.

In extreme examples, the course is obvious, as in the case of subdural block and cardiac arrest described by Rowbottom and colleagues [1]: Caesarean section was performed during (successful) resuscitation. In lesser cases, many would, as Rowbottom suggests, abandon regional techniques; however, we have found subdural blocks, when recognized, to be somewhat similar to subarachnoid blocks in being fairly predictable in their onset and spread, and injection of small doses of local anaesthetic (0.5–2 ml), with or without opioid, with careful monitoring usually provides safe and efficient analgesia or anaesthesia [2].

The alternative management in the case of Caesarean section is to opt for general anaesthesia, with its attendant risks, including severe bradycardia and even asystole in patients given suxamethonium in the presence of high sympathetic block. Furthermore, another cause for concern about combined techniques has been brought to our attention recently, after two cases of maternal deaths in our area. These resulted from anaphylactic reactions to suxamethonium in patients who had extradural blocks in place. Both patients were reported as being "extremely difficult to resuscitate". To resort to general anaesthesia in a patient with an atypical block may introduce new hazards that could have been avoided by careful "tailoring" of the block to the patient's needs.

Finally, we cannot agree that terminal eye catheters confer any greater degree of safety than lateral eye catheters and, indeed, they may be less safe. We have just concluded a study comparing the two types, and recorded one case of intravascular injection, through a terminal eye catheter, despite repeated negative attempts at aspiration. The ability to allow easy aspiration of blood or CSF has always been claimed to be the main advantage of the terminal eye catheter [3].

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1. Rowbottom SJ, Kong AS, Chan M, Tabrizian I. Subdural block. *Anaesthesia and Intensive Care* 1993; **21**: 132–133.
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COMPARISON OF TWO MEASUREMENTS

Sir,—I read with interest Dr Runcie's letter [1] concerning the article by Berridge which described the influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation [2]. Dr Runcie correctly pointed out that the statistical analysis of the data should examine the difference between mixed venous and central venous oxygen saturation and not the correlation between them. However, as has been noted previously [3], the original Bland–Altman technique [4] is not invariably an appropriate method for comparing two measurements: it is intended to determine the agreement between two methods of clinical measurement of a variable, when neither of the methods is sufficiently accurate to be considered a "gold standard". In this method, the difference between the measurements is plotted against the mean of the two measurements, the mean of the measurements (rather than one or other of the two) being used as the independent variable for two reasons:

(1) When both measurements are subject to an unknown error, the best estimate of the true value of the variable is the mean of the two measurements [4]. This is not likely to be the case with Berridge's data: the measured mixed venous oxygen saturation is almost certainly a better measure of the true mixed venous oxygen saturation than is the mean of the central venous and mixed venous saturations.

(2) It is a well known statistical phenomenon that, if the difference between two values is plotted against one or the other, the difference is related to each of them [4]. For example, the expected correlation coefficient between the difference between

two uncorrelated variables (which have equal variance) and each of them is approximately 0.71 [5]. However, no correlation will be expected between the difference between the variables and the mean of them [5].

The practical importance of the above depends upon the magnitude of the experimental error in the variables. If one is known to be the true value (i.e. it is not subject to any experimental error), regression of the difference between the variables on this (true) variable may be expected to estimate correctly the correlation and regression coefficients of the difference between the variables on the true variable. However, if, as is usually the case in clinical investigation, there is error in both variables and the investigator is interested in the regression of the difference on the true (rather than the observed) value, one is presented with the common problem of errors in the independent variable. If the variance of the error in the independent variable is known, the best estimate [$\hat{b}$] of the regression coefficient of the difference on the true value of the independent variable can be calculated from the regression coefficient of the difference on the measured value of the independent variable [$\hat{b}'$] using the method described by Blomqvist [6]:

$$\hat{b} = (\hat{b}' + \lambda)/(1-\lambda) \qquad (1)$$

where λ is the ratio of the error variance to the total variance of the independent variable.

The latter point may be illustrated by considering data from an imaginary experiment in which the outputs of two (equally imaginary and somewhat unsatisfactory) pulse oximeters are compared with each other and with values of arterial blood oxygen saturation determined from blood samples analysed *in vitro* using a multiwavelength oximeter. For the purposes of this discussion, it is assumed that (1) the *in vitro* oximeter has a precision (εa) of 0.5% and (2) both pulse oximeters are subject to (a) a linear systematic error ranging from 0% at an arterial saturation of 100% to +10% at an arterial saturation of 75%, and (b) random errors (εp) with an SD of 2.5% around this systematic error. That is to say, the measured arterial saturation (*S*a) is related to the true saturation (*S*) by the equation:

$$S\text{a} = S + \varepsilon\text{a} \qquad (2)$$

and the difference between the saturation measured by the pulse oximeters (*S*p) and the true saturation for both pulse oximeters is related to the true saturation by the equation:

$$S\text{p} - S = S - 0.4.(S - 100) + \varepsilon\text{p} \qquad (3)$$

Inspection of the data for one of the pulse oximeters ($S\text{p}_1$) plotted against the measured arterial saturation (fig. 1) suggests that, as would be expected from equation (3), the pulse oximeter tends to overestimate the arterial saturation, and that the error increases as saturation decreases. Since *S* is unknown, the differences between the various measured values of saturation may be analysed in a number of ways:

(1) Regression of $S\text{p}_1$ on *S*a (fig. 2). The slope of the regression line (−0.387 (0.065)) is significantly different from 0 ($P < 0.001$), and is not significantly different from the true value of −0.4 ($P = 0.846$). The investigator would conclude correctly that the error of the pulse oximeter increased as the arterial saturation decreased. The effect of Blomqvist's adjustment is small, owing to the small error variance in *S*a (0.25) compared with the total variance (19.1), the adjusted slope being −0.378 (0.066).

(2) Regression of $S\text{p}_1 - S\text{a}$ on the mean of $S\text{p}_1$ and *S*a (Bland–Altman method, fig. 3). The slope of the regression line (−0.138 (0.086)) is not significantly different from 0 ($P = 0.114$). This would lead to the incorrect conclusion that the bias of the pulse oximeter (estimated from the mean and SD of $S\text{p}_1 - S\text{a}$, 5.9 (3.3)%) was unaffected by the actual arterial saturation.

(3) Comparison of the differences in the output of the two pulse oximeters by regression of $S\text{p}_2 - S\text{p}_1$ on $S\text{p}_1$ (fig. 4). The slope of the regression line (−0.525 (0.074)) is significantly different from 0 ($P < 0.001$), which would indicate incorrectly that a systematic difference existed between the output of the pulse oximeters. It is this type of spurious association that is avoided by use of the Bland–Altman method.

(4) Regression of $S\text{p}_2 - S\text{p}_1$ on $S\text{p}_1$ using Blomqvist's adjustment (fig. 4), the error variance in $S\text{p}_1$ being 6.25 (from εp above) and the total variance in $S\text{p}_1$ being found to be 15.1. The adjusted slope of the regression line (−0.190 (0.171)) is not significantly different from 0 ($P = 0.270$). This is consistent with our model, in which the output of the pulse oximeters does not differ except for random variation.

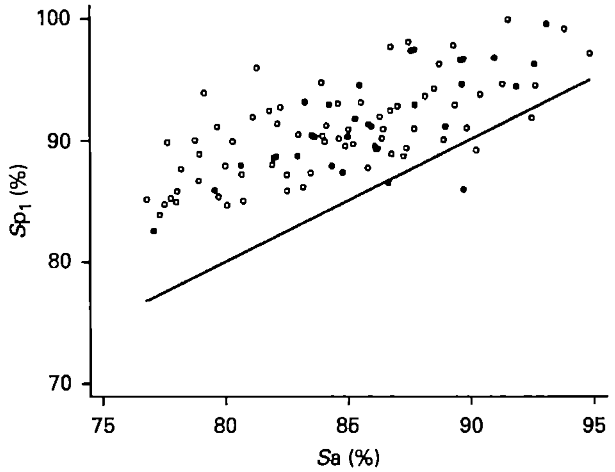

FIG. 1. Plot of arterial blood oxygen saturation measured by one pulse oximeter ($S\text{p}_1$) against saturation measured by the *in vitro* oximeter (*S*a), with the line of equality.

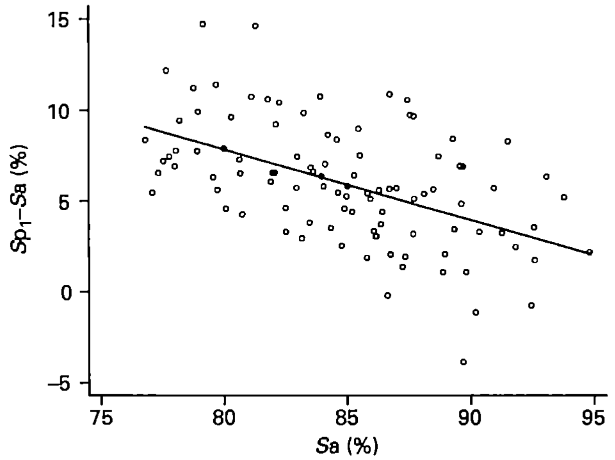

FIG. 2. Plot of the difference between arterial blood oxygen saturation measured by one pulse oximeter and that measured by the *in vitro* oximeter ($S\text{p}_1 - S\text{a}$) against saturation measured *in vitro* (*S*a), with the regression line.

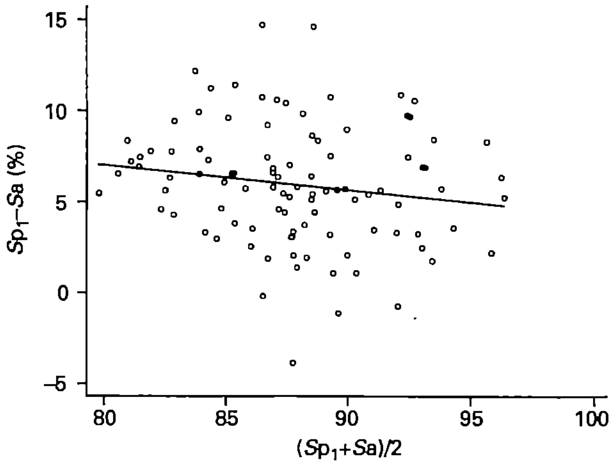

FIG. 3. Plot of the difference between arterial blood oxygen saturation measured by one pulse oximeter and that measured by the *in vitro* oximeter ($S\text{p}_1 - S\text{a}$) against the mean of the two saturations (($S\text{p}_1 + S\text{a})/2$), with the regression line.

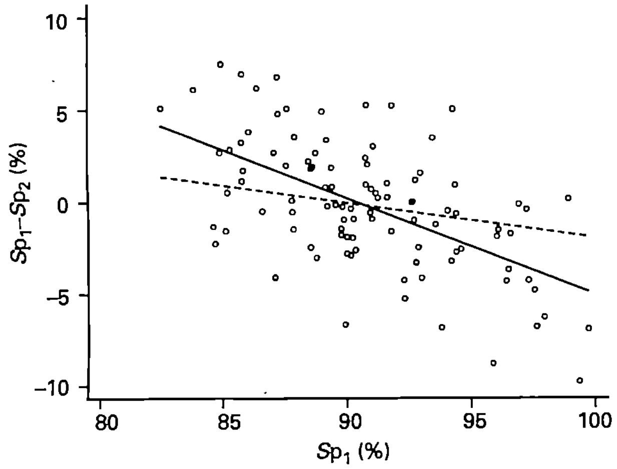

FIG. 4. Plot of the difference between arterial blood oxygen saturation measured by the two pulse oximeters ($Sp_2 - Sp_1$) against the saturation measured by one of them (Sp_1). The solid line represents the ordinary regression line, the dashed line represents Blomqvist's adjustment.

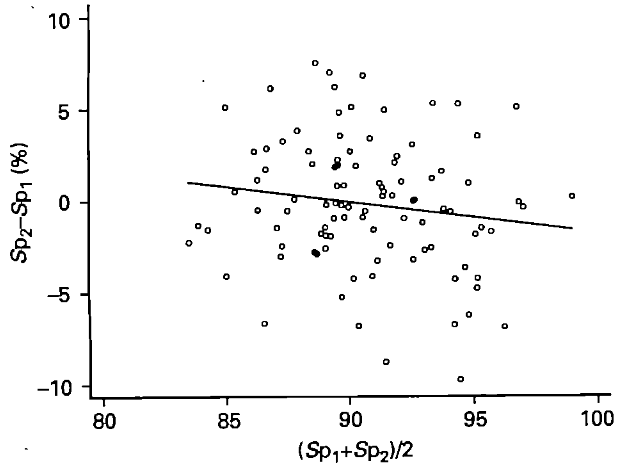

FIG. 5. Plot of the difference between arterial blood oxygen saturation measured by the two pulse oximeters ($Sp_2 - Sp_1$) against the mean of the two saturations (($Sp_1 + Sp_2$)/2), with the regression line.

(5) Comparison of the output of the two pulse oximeters by regression of $Sp_2 - Sp_1$ on the mean of Sp_2 and Sp_1 (Bland–Altman method) (fig. 5). The slope of the regression line (−0.171 (0.109)) is not significantly different from 0 ($P = 0.120$), which is again consistent with our model.

It is important, therefore, to consider the accuracy of each method before comparing the measurements using the Bland–Altman method. It is appropriate for the purpose for which it was described—that is, to assess the degree of agreement between two methods of clinical measurement of a variable where the true values remain unknown [4, 7]. However, if one of the methods of measurement is sufficiently accurate to be considered a "gold standard", the conservative nature of the Bland–Altman method may lead to its failure to detect true systematic differences between the methods.

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ANAPHYLACTOID OR CARCINOID CRISIS?

Sir,—We read with interest Batchelor's paper reporting a case of cardiovascular collapse, with tachycardia followed by bradycardia, marked ST depression and flushing of the upper part of the body. Symptoms started several minutes after i.v. injections of alfentanil, propofol and suxamethonium. A radioallergosorbent assay (RAST) to suxamethonium was clearly positive in this patient who had previously received three other neuromuscular blocking drugs [1].

The authors speculated if these features indicated anaphylaxis to suxamethonium, or carcinoid crisis, as the concentration of 5-hydroxyindoleacetic acid (5HIAA) in the first urinary sample was increased and the patient had carcinoid tumour.

We wish to stress three points. First, we agree with Watkins that the RAST to suxamethonium is not specific for quaternary ammonium ions [2]. In this case, it would be worth obtaining this evidence, as the patient had previously received neuromuscular blockers other than suxamethonium. Two radioimmunoassays specific for quaternary ammonium ions are available in France [3, 4]. They may be complemented by inhibition tests with the myoneural blockers, demonstrating that specific IgE directed towards quaternary ammonium ions exist, and they are able to cross-react with different neuromuscular blockers. It may be hypothesized that this woman was sensitized by either alcuronium or pancuronium–vecuronium, and had an anaphylactic cross-reaction to suxamethonium. It may be expected that she had no cross-reactivity with atracurium, as she tolerated this drug well. Skin prick-tests would test this hypothesis beyond doubt [5].

The point that worried the authors was the increased concentration of urinary 5HIAA, which may have been released from the carcinoid tumour. However, we have shown that human platelets from patients sensitized to myoneural blockers are able to release serotonin, when incubated with the blocking drug [6]. There is therefore good presumptive evidence for an increment of 5HIAA in the course of anaphylaxis. Moreover, nothing is known about the release of mediators from carcinoid tumours, during simultaneous anaphylaxis [7]. Could the release of vasoactive mediators be dependent on an IgE-triggered mechanism?

Finally, the severity of the anaphylactoid shock suggests double anaphylaxis incriminating propofol. Indeed, we have verified that, of 14 patients having a life-threatening reaction within minutes after receiving propofol, four had IgE specific not only to propofol, but also to neuromuscular blocking drugs. This astonishing fact remains unexplained [8]. We suggest, therefore, that anaphylaxis to propofol be sought in this very interesting case.

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Sir,—The above authors raise three main points.

First, is our patient sensitive to other neuromuscular blockers? They agree with Watkins [1] that the RAST for suxamethonium is not specific for quaternary ammonium groups, but is specific for the agent. Sensitization to this drug despite no previous exposure could be either via sensitization by other neuromuscular blockers or by exposure to other agents containing quaternary ammonium groups, such as food or cosmetics. We have not carried out skin tests on our patient, so are unable to clarify this point.

Second, the increased concentration of 5HIAA in urine noted in our patient, particularly on the first day after operation. We note the authors' recent work on platelet release of serotonin [2]. Serotonin produces bronchospasm, which was not a feature in our patient. The urinary concentrations of 5HIAA were increased only slightly, and it is speculative to suggest this was caused by either platelet or tumour release of serotonin.

Third, the authors suggest the severity of the anaphylactoid reaction signifies a double aetiology. Anaphylaxis to suxamethonium has proved fatal [3], so we cannot agree with this hypothesis. The reported incidence of anaphylaxis to propofol is 1:60000 and that to neuromuscular blockers 1:6000 [4] and the chances of one patient having antibodies to both drugs despite no previous exposure to either must be very small. Indeed, the authors themselves note that only five cases have been reported in the world literature [5, 6], although one did appear to be caused by both propofol and suxamethonium.

Our patient was interesting as the cause of the cardiovascular collapse could have been either an anaphylactoid or carcinoid reaction, and the dilemma was produced because the patient required a second anaesthetic. We see very few reactions to anaesthetic drugs and do not subsequently subject our patients to either prick or intradermal testing. The case for testing for sensitivity to neuromuscular blocking drugs seems sound with a high specificity, sensitivity and reproducibility [7], but is not so convincing for induction agents, including propofol. Should we have further tested our patient when we already had two possible causes for her collapse—and, do others test in this situation?

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"XYLOCAINE" SPRAY AND LARYNGEAL OEDEMA

Sir,—I have an experience similar to that experienced by Dr Taylor [1] using Xylocaine Spray new formulation with cats.

It involved a child with a permanent tracheostomy for tracheomalacia who had regular bronchoscopy/laryngoscopies. With the first use of the new formulation spray, his larynx became grossly oedematous within minutes.

At a later date the procedure was repeated with the old formulation, with no problems.

I have not used the new spray since this episode.

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HEPATOTOXICITY OF VOLATILE ANAESTHETIC AGENTS

Sir,—The review article on "Hepatotoxicity of volatile anaesthetics" [1] expressed some speculative views on the incidence and aetiology of hepatic failure after volatile anaesthesia, and went on to make comments on the medico-legal implications of repeat exposure to halothane.

I have an alternative, if somewhat heretical, interpretation of the available evidence on these matters, which is markedly different from those expressed in this review article. Halothane hepatitis is rare, and death from this cause was found to be 1 in 110000 halothane anaesthetics in a study reported by the Swedish Adverse Drug Committee [2]. This is an incidence three times less than the 1 in 35000 found in the National Halothane Study, and quoted by the authors of the review article. The incidence of halothane hepatitis is at best an educated guess, as the epidemiological aspects of this condition have been sadly neglected.

If a patient has had a previous halothane anaesthetic, there is no evidence to support the contention that the overall safety after anaesthesia with a non-halothane technique is associated with a lower incidence of catastrophic anaesthetic events than when halothane is used. A prospective, controlled trial assessing all catastrophic anaesthetic complications, comparing halothane, isoflurane, desflurane, ethrane, sevoflurane and opioid-based anaesthetic techniques would be required before specific recommendations could be made rationally. In the National Halothane Study [3], halothane had a smaller incidence of catastrophic complications than most other volatile agents assessed in the trial. A multicentre, prospective, randomized clinical trial studying 17201 patients was reported in 1990 [4, 5], in which serious adverse outcomes after general anaesthesia with enflurane, fentanyl, halothane or isoflurane were compared. In the halothane group, there were fewer deaths, although this was not statistically significant, and the smallest incidence of myocardial ischaemia and respiratory/laryngeal complications. If a more pungent, irritant volatile anaesthetic is substituted for sweet smelling halothane, then death from hypoxia, secondary to laryngospasm, bronchospasm, airway obstruction and aspiration [6–8] may occur with a greater frequency than hepatic failure after halothane.

The authors of the review make recommendations regarding the propriety of using repeat halothane which lack scientific validity. My view is that, for the patient breathing spontaneously via a face mask, repeat anaesthesia with halothane is simpler, easier and safer than repeat anaesthesia with any other currently available anaesthetic agent. Not only is the use of repeat halothane defensible, from a medico-legal viewpoint, it is at times the preferred option.

Scientists studying the effects of anaesthetic agents on liver function have been mesmerized by irrelevant intermediate events (such as minor fluctuations of serum enzymes, which have never been shown to have clinical relevance [9]) rather than catastrophic anaesthetic complications. What needs to be compared between the different anaesthetic agents is the different incidences of life-threatening, catastrophic events: liver failure, hypoxic brain damage, respiratory failure, renal failure, seizures, etc., which cause major morbidity and, occasionally, mortality. Research on the hepatic effect of halothane in rats, mice, guineapigs and rabbits, although voluminous, has never been shown to be relevant to the human conditions of catastrophic hepatic failure after halothane.

Currently there is a vogue promulgating antibodies as the cause of hepatic failure after halothane [10]. If this were the case, antibodies from a patient with the condition, when injected into an animal recently anaesthetized with halothane, should induce liver failure in that animal. This has never been demonstrated, with the logical conclusion being that antibodies do not cause halothane-induced liver disease. Proponents of the antibody test to diagnose halothane-induced liver disease claim that 80% of patients with the condition have the antibody. What causes the disease in the 20% of patients without the antibody?

Another theory to explain halothane-induced liver disease involves the production of toxic intermediates [11], although no such intermediates have been shown to be uniquely produced by patients who develop halothane hepatitis. Halothane metabolic intermediates are produced in the same quantitative and qualitative manner by patients without increased serum liver enzymes as by those patients who die of fulminant hepatic failure. If the theory that metabolism of halothane causes halothane hepatitis is unfounded, then to suggest that an agent which is metabolized less than halothane will be associated with a smaller incidence of hepatic failure lacks a scientific basis. The authors of the review proffer an incidence of fulminant hepatic failure after isoflurane anaesthesia approaching 1 in 3500000 anaesthetics, based on an incidence of halothane hepatitis of 1 in 35000 and the fact that isoflurane is metabolized at least 100-fold less than halothane. This speculation seems rather fanciful. Why is it that halothane hepatitis is a medical curiosity in children [12]? Why is it that halothane hepatitis can occur after a single halothane anaesthetic and for the first time after eight halothane anaesthetics [13]? Why is it that some patients who have had halothane hepatitis, when re-exposed to halothane do not get the disease [14]? Why is it that lethal hepatic failure has been reported after virtually all known anaesthetic agents [15–19]? The answers to these questions remain unknown.

There has been much pontification, rhetoric and academic arrogance in the halothane hepatitis debate. The available epidemiological evidence on anaesthetic mortality does not support the contentions, based on case reports, reports of a few cases and laboratory investigations in animals, that repeat halothane anaesthesia is associated with a greater incidence of catastrophic complications than repeat anaesthesia when other agents and techniques are used [20]. As the boy said in the Hans Christian Andersen story, "Look, Mummy, the Emperor has no clothes".

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Sir,—It is correct that the true incidence of halothane-associated hepatitis (HAH) is unknown but rare, and we agree also that some aspects of HAH have been neglected, particularly as alternative agents have become available. However, in the absence of diagnostic tests and pathology, the diagnosis of HAH used to be difficult to confirm. This should not now be the case, with the present increased awareness and ability to diagnose many other types of hepatitis. We encouraged the taking of a full history and examination and the use of many laboratory tests, including the trifluoroacetyl (TFA)-antibody test, to enable a more accurate incidence of HAH to be determined and in order that the TFA-antibody test may be quantified. Few tests are 100% specific and we are sure that the specificity of the TFA-antibody test will be improved, as it already has been since its introduction [1, 2].

Our review concentrated on the hepatotoxicity of volatile agents, and we accept that the hepatotoxic effect of any anaesthetic agent will be only one of the risk factors to be considered in the choice of anaesthetic technique. In certain cases, it may be possible that the balance of risks favours the repeated use of halothane over the alternatives available. We note that the studies mentioned by Dr Wark [3, 4] did not show any statistically significant benefit from using halothane.

The exact reasons why some patients develop fatal hepatic failure after repeated halothane exposure while most do not, are still unclear, but HAH is recognized sufficiently that warnings against the repeated use of halothane are included in the manufacturer's data sheet for halothane [5]. It seems sensible to us to ignore such advice deliberately only in circumstances in which halothane is indicated specifically. These may include those in which "...economic factors and availability of trained personnel are the primary determinants of clinical practice" [6]. Otherwise, one may leave oneself very much exposed.

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PRESSOR RESPONSE TO VENOUS CANNULATION

Sir,—Langham and Harrison, in their study of the attenuation of the pressor response to cannulation by subcutaneous lignocaine [1], reach the correct conclusion but for the wrong reason. We should use local anaesthesia before inserting i.v. cannulae because it hurts and patients do not like it; the pressor response is of no clinical consequence.

The investigators take the parallel of the pressor response to intubation of the trachea, but are selective in their references to earlier work, and quote research in which various physiological variables were measured. In an editorial, Thomson [2] pointed out that physiology is not outcome, and that there are reasons to doubt the suggestion that preventing ischaemia at the time of intubation might prevent infarction in patients with ischaemic heart disease. We must be wary of making too much of physiological descriptions. In justifying the need for cardiovascular stability, Langham and Harrison wrote "even healthy patients may suffer depression of left ventricular ejection fraction", but where is the evidence to justify the implication, in the use of the word "suffer", that these healthy patients were harmed by the change?

Thomson accepted that there is a small subgroup whom all agree should be protected even from a single hyperdynamic episode. Outside this subgroup, it is an equally valid hypothesis that the pressor response to intubation is useful because it reverses the hypotension of induction of anaesthesia. Even within this statement there is an unproven assumption: that the hypotension of induction affects outcome, except in another and probably different subgroup. There is indeed, as Langham and Harrison stated, a large volume of published research on the pressor response, and it is out of all proportion to its importance in anaesthesia. Does it reflect the ease with which the physiological measurements can be made at that period in the conduct of an anaesthetic? With the large number of available combinations of induction agents, local anaesthetics, opioids, beta-adrenoceptor antagonists, and now alpha$_2$-adrenoceptor agonists, there is still scope for many more studies, but to what purpose?

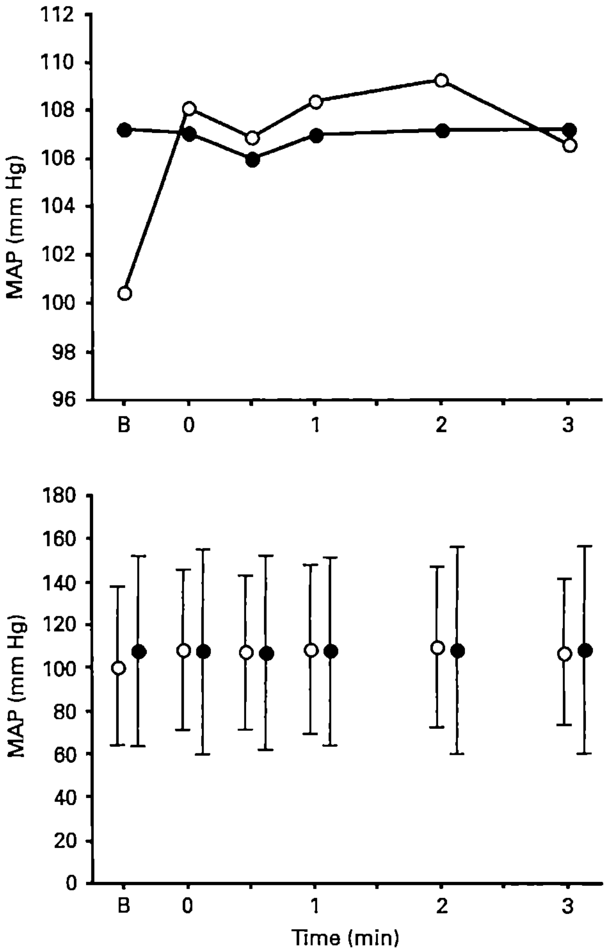

FIG. 1. Upper panel: mean arterial pressure with time (means only, expanded scale). Lower panel: mean arterial pressure with time (means and 2 SD, full scale). B = Baseline measurement. ○ = Cannulation without local anaesthesia; ● = cannulation after infiltration with lignocaine. (Data from [1].)

On Langham and Harrison's evidence, there is even less need for study of the pressor response to cannulation. The correct conclusion from their clear results is that there is a pressor response, and it is clinically unimportant. They describe "significant increases in [mean arterial pressure] ($P < 0.01$) and in [rate-pressure product] ($P < 0.01$)". The upper panel in figure 1 (Langham and Harrison's figure) shows an impressive difference between the group who had lignocaine infiltration and the group who did not, but the graph exaggerates the findings because the Y-axis is of *change* in mean arterial pressure, and is on an expanded scale.

From the error bars on the graph (which represent the standard error of the mean), a rough calculation of the standard deviation suggests that the largest increase in mean arterial pressure in the control group was about 28 mm Hg, and that in the lignocaine group about 14 mm Hg. The maintained mean difference between the groups was 8 mm Hg. This increase was statistically significant, and the investigators thought it clinically important, but there was a difference of almost as much (6.7 mm Hg) between the baseline readings of the two groups, even though this was statistically insignificant.

The findings are clearer if presented as absolute values. With an expanded Y-axis, the baseline difference becomes apparent (fig. 1, upper panel); with a more conventional scale to the Y-axis, and with error bars of 2 SD, the results may be seen in perspective (fig. 1, lower panel).

The investigators described repeat testing for differences between the groups by Student's unpaired *t* test or by Mann–Whitney *U* test, and stated that they then *confirmed* the differences by analysis of variance or by Kruskal–Wallis. However, it is invalid to test repeatedly by Student's or by Mann–Whitney *unless* a difference between groups *has first been shown* by analysis of variance or by Kruskal–Wallis.

The investigators' final assertion is unproven. They imply that a patient who has already had a pressor response to cannulation may have an exaggerated response to a further stimulus, and that this is the reason that high risk patients should receive local anaesthesia before cannulation. The investigators did not describe subsequent laryngoscopy, so do not know that a response would be exaggerated. Patients truly at high risk would almost certainly receive some prophylactic treatment before laryngoscopy, and "will never be included in the control group of an outcome study examining the efficacy of haemodynamic control at... intubation!" [2].

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1. Langham BT, Harrison DA. The pressor response to venous cannulation: attenuation by prior infiltration with local anaesthetic. *British Journal of Anaesthesia* 1993; 70: 519–521.
2. Thomson IR. The haemodynamic response to intubation: a perspective. *Canadian Journal of Anaesthesia* 1989; 36: 367–369.

Sir,—In the paper by Langham and Harrison on the pressor response to insertion of an 18-gauge venous cannula [1], the authors concluded that there was a significant response to venous cannulation, as judged by changes in mean arterial pressure (MAP) and rate–pressure product (RPP), which was obtunded by prior infiltration with local anaesthetic; they recommended that lignocaine should be considered before insertion of an i.v. cannula. There are several aspects of this paper which we would like to discuss further.

First, we were not told in which arm cannulation took place. Presumably, it was into the arm opposite to that used for arterial pressure readings. Injection of local anaesthetic into the same arm might, theoretically, affect the neighbouring microvasculature and interfere with arterial pressure readings by digital plethysmography. Second, we were not told if the cannulation site was standardized. It is possible that bias could have occurred if Investigator 1 was free to choose a location for cannulation. The methodology described does not prevent Investigator 1 using a large antecubital vein for one group and a small ventral wrist vein for the other. Third, the reader is unable to determine if patient bias influenced outcome. What information was the patients given? Were they aware that they would receive either a single injection or two and over what time scale? The study would have been more powerful if it had included a placebo group given saline before cannulation. Fourth, precisely which moment was taken as time zero? Was this at the beginning of cannulation (or local infiltration), during or immediately after? If time zero was taken as the start of local infiltration, what was the pressor response to insertion of the 25-gauge needle? Finally, and most importantly, the authors state that there was no significant differences between the two groups in baseline readings of MAP or heart rate (HR). This is strictly true, but it might have been more reasonable to state that there were differences in baseline values for MAP and HR, but that these were not statistically significant. Analysis of baseline values in Langham and Harrison's table I using Student's *t* test reveals that, in the local infiltration group, MAP was 6.6% greater (P 0.5–0.1) and HR was 10.7% greater (P 0.1–0.05). However, the baseline RPP was 14.7% greater and this was statistically significant ($P < 0.05$)—a point which the authors did not discuss. We would like to suggest that this difference in baseline RPP undermines the conclusions of this paper.

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1. Langham BT, Harrison DA. The pressor response to venous cannulation: attenuation by prior infiltration with local anaesthetic. *British Journal of Anaesthesia* 1993; 70: 519–521.

Sir,—Dr Goodman will be aware that the order in which statistical tests are performed has no influence on the interpretation of results. The differences were apparent when analysis of variance or Kruskal–Wallis were performed; the Student's unpaired *t* test and Mann–Whitney *U* test identified the times at which these differences occurred.

It is recognized that, despite random allocation, cardiovascular variables may differ when baseline recordings are made in two groups of patients. The technique of normalizing data by analysis of change from the baseline value is well recognized and this technique was used because of the difference in baseline values and not because of any intention to exaggerate differences between the groups.

Dr Brimacombe and his colleagues have drawn to our attention an omission in our paper; they stated correctly that site of cannulation was not noted. The cannulation site was standardized, being the dorsum of the non-dominant hand. The Finapres monitor was sited on the middle finger of the contralateral hand; any proposed effect on the "neighbouring microvasculature" of the local anaesthetic infiltration would therefore not be relevant. Consent was obtained from the patients on the night before surgery, at which time they were told that they may receive one or two "scratches" in the back of their hand. As clearly stated in the paper, time zero was taken as the time of the first stimulus to the patient, be it local infiltration or cannula insertion. The lack of a pressor response to the insertion of the 25-gauge needle is apparent from the results presented.

We agree with Dr Goodman that the most important reason to use local anaesthetic infiltration before venous cannulation is humanitarian and our previous studies [1, 2] had already addressed this issue. The fact that a measurable pressor response occurred in normal patients may imply that a clinically important response occurs, for example in those with pre-existing hypertension, and this is currently being studied.

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1. Harrison N, Langham BT, Bogod DG. Appropriate use of local anaesthetic for venous cannulation. *Anaesthesia* 1992; 47: 210–212.
2. Langham BT, Harrison DA. Local anaesthetic: does it really reduce the pain of insertion of all sizes of venous cannula? *Anaesthesia* 1992; 47: 890–891.

THE MANAGEMENT OF ACUTE POISONING

Sir,—We read with interest the review article by Collee and Hanson [1], but wish to raise a number of points. We would question the statements that "in unconscious patients organic brain damage should always be suspected if the history of poisoning is unsatisfactory and the depth of the coma does not improve within 12 h" and that "any patient whose level of consciousness appears inappropriately depressed for the history of the poisoning should be suspected of having an intracranial haemorrhage." In our experience, a satisfactory history of the poisoning in an unconscious patient is rare. In this situation it is essential to exclude a correctable metabolic or intracranial cause for the coma. Even in the presence of a good history, a high degree of suspicion should be maintained; intoxicated patients are often the victims of trauma. It is mandatory to exclude intracranial pathology before ascribing a depressed state of consciousness to the effects of drugs or alcohol. With appropriate neurological examination and the ready availability of CT scanning, we have the means to avoid repeating the lessons of the past [2].

From our experiences with intoxicated patients in North American hospitals, we recognize that the agitated, aggressive, stuporous or comatose intoxicated patient poses many problems in assessment and treatment. Under these circumstances an aggressive approach to patient management may be appropriate. Rapid sequence induction, tracheal intubation and control of ventilation prevent the patient injuring themselves or others, reduces the chance of secondary brain injury, facilitates investigation (CT scanning), allows monitoring of vital signs and provides optimal conditions for any intervention.

Second, we were surprised that the review did not mention the possible use of dantrolene in the management of hyperthermia associated with acute intoxication. The role of this drug in the treatment of hyperthermia secondary to intoxication has been underestimated in the past, but many recent reports of its use in this potentially fatal complication suggest that it may lead to improved outcome [3, 4].

Third, the list of cardiovascular complications of acute poisoning does not include myocardial ischaemia or infarction; these are serious omissions. Reports of more than 50 cases of acute myocardial infarction complicating poisoning have been published. Seventy percent of the victims had no significant cardiac history, the majority being young males who were regular users of cocaine [5]. Recognition of this potential complication has direct consequences on the choice of agents used to manage the cardiovascular complications of cocaine intoxication. Cocaine produces postsynaptic accumulation of catecholamines, resulting in increased sympathetic nervous system effects. Lignocaine is an illogical choice as an anti-arrhythmic in this situation: in common with cocaine, it is also a local anaesthetic and decreases the seizure threshold, and may precipitate convulsions. Propranolol is also an illogical choice; beta block alone may result in unopposed alpha adrenoceptor activity, thus worsening coronary vasoconstriction and hypertension [6]. There are two logical choices available for controlling the cardiovascular effects of cocaine toxicity: labetolol, which the authors did mention, and esmolol, a beta$_1$-adrenoceptor (cardioselective) blocker; both have been reported as being of use in cocaine toxicity [7, 8].

Finally, we were confused by the advice given for the treatment of salicylate poisoning. The fluid regimen called for 1 litre of saline 1 mol litre^{-1} or 0.3 mol litre^{-1} every 4–6 h, but that one should *not give more than 300 mmol of sodium per 24 h (sic)*. The initial instruction would result in the administration of 1000 mmol of sodium. One litre of 0.3 mol litre^{-1} every 4–6 h would provide 1800–1200 mmol of sodium in 24 h, both prescriptions providing considerably more than the stipulated maximum dosage.

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1. Collee GG, Hanson GC. The management of acute poisoning. *British Journal of Anaesthesia* 1993; **70**: 562–573.
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Sir,—Thank you for the opportunity to reply to this letter.

The critique of our article by Drs Parr and Craft is helpful, and we agree with several of the issues they raise. Certainly the exclusion of intracranial pathology in cases of acute coma is mandatory, but the circumstances in which an "aggressive approach" to patient management is justified are difficult to define precisely. Clearly, a full clinical assessment by appropriate specialists is preferrable to a blanket policy of CT scanning.

Regarding the role of dantrolene in the management of hyperthermia following acute intoxication, we feel insufficient evidence exists at present to recommend its use. In addition to the two case reports cited in the letter from Drs Parr and Craft [1, 2], we discovered only two others before submitting our manuscript [3, 4]. Hyperthermia occurring after 3,4-methylenedioxymethamphetamine—"Ecstasy"—may be related to its effect on central serotonergic and dopaminergic pathways, or to the circumstances of its abuse. The mechanism is not yet known. The prolonged exercise and dehydration resulting from all-night dancing suggest that, in many cases, hyperthermia after Ecstasy may resemble heatstroke in its pathogenesis. Such cases would not be expected to respond to dantrolene [5], nor do the central mechanisms provide an easy explanation of why dantrolene should be expected to be an effective treatment if neuromuscular blockers fail. In one report of its use [3], an initial dose of 1 mg kg^{-1} failed to reduce the patient's temperature, which remained increased until after a third dose. Dr Parr's own case report of the use of dantrolene in the treatment of a fatal theophylline overdosage remains (as far as we know) the only account of its use in hyperthermia of that aetiology. It seems prudent to await further results. Meanwhile, we feel it more appropriate to emphasize the importance of general supportive measures.

We thank Drs Parr and Craft for pointing out the omission of myocardial ischaemia in the general section on the cardiovascular complications of acute poisoning. Regarding the management of arrhythmias secondary to cocaine poisoning, the role of beta$_1$ antagonists is undisputed.

The fluid regimen in salicylate poisoning was converted to S.I. units in accordance with editorial guidelines, and it is indeed confusing. An erratum appeared in the August issue of *British Journal of Anaesthesia* (p. 331).

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BOOK REVIEWS

Whose Life Is It Anyhow? By S. L. Cohen. Published by Robson Books, London. Pp. 206; indexed. Price £16.95.

It would not be sensible to review this book as if it were a medical text, as it is aimed at the general public. Nevertheless, certain points can be made.

Its intent is to engage the public in debate about some of the most pressing problems in medicine—namely, the ethics of applying "high tech" medicine to patients, some of whose quality of life, at best, can only be poor—while at the same time emphasizing the cost-benefit equation.

The book is certainly topical and includes a brief discussion of the problems which surrounded the management of the Tony Bland case. It also outlines the current state of affairs concerning living wills and self determination, questions which require a wide range airing and public debate.

I do not know if the public will feel better informed after reading it. I am afraid I felt rather unhappy about the manner in which some dramatic and tragic cases were described. The author seemed to want to ask the public what they would do while, inevitably, not giving them a forum in which to reply. In so doing, he could probably increase the population's anxieties about what he implies was a random chance of being denied therapy or of having it discontinued inappropriately.

Inevitably, as it is for general readership, the slant of the book is towards drama and difficulty and excludes the more mundane and routine aspects of intensive therapy. Because of this, I do not believe it helps to clarify what are, in fact, serious problems, despite the good intentions of the author and the mobilization of a number of erudite ethical opinions.

The doctor who is engaged in intensive therapy, or indeed in any branch of medicine where such pressing problems arise, will find references to philosophical and religious authorities which he might not otherwise know of. Apart from this I believe, like myself, he will feel slightly irritated and a little disappointed at a missed opportunity for public information and education.

J. C. Stoddart

Principles and Practice of Medical Intensive Care. Edited by R. W. Carlson and M. A. Geheb. Published by W. B. Saunders Company, Philadelphia. Pp. 1796; indexed; illustrated. Price £136.00.

At last, the specialty of Intensive Care has a textbook equivalent of Harrison's *Textbook of Internal Medicine.* With almost 2000 pages and 149 chapters, this is a comprehensive textbook of current intensive care practice. The general layout of the book is easy to follow and the general tone of the chapters is similar to that found in the larger general medical textbooks, with comprehensive reviews of the topic and, in general, avoidance of the didactic statements about management which tend to feature in the smaller handbooks of intensive care. The standard of the chapters is extraordinary. Almost every chapter would stand alone, or at least with its companion chapters, as definitive reviews of the particular topics.

Unusual but useful chapters were those on prehospital care and disaster management. The medical aspects of intensive care were extremely well reviewed and the section on sepsis was exceptional. This latter section was particularly interesting because of the balanced views of the authors.

Referencing is not excessive, and references chosen are generally relevant, useful and as up-to-date as can be expected of a book of this size and complexity. I found the index easy to use and effective. There are a large number of diagrams and the chapter on imaging has remarkably good reproduction of x-rays. There are of course some negative aspects to the book. The introduction has a very heavy U.S. bias and one could almost imagine that intensive care grew solely in the United States, but then it is an American book.

Apart from that, it is difficult to find problems with most of the chapters. One did stand out as being mediocre as opposed to excellent and that was the chapter on obstetrics, which fell into the trap of being didactic in terms of management regimens and had a simplistic approach to the subject, rather than the usual review style of other chapters. Had it been written in the same style and with similar depth as the others, it would have been a useful addition to a subject covered surprisingly poorly in the ITU literature. The other chapter that I found disappointing was that on neurosurgical trauma and spinal cord injury, which was very superficial in approach, but this may reflect the medical bias of the book. Some chapters had unexpected omissions of recent, rather than new, topics which may be a reflection of the time taken to compile the book; for example, there was very little on the use of veno–venous pumps in continuous renal support. Having said that, the rest of that chapter was very good.

These criticisms are minor, and the book is an outstanding addition to the intensive care literature. I have always felt it useful to have a copy of Harrison's *Internal Medicine* in the intensive care unit, but this book now makes it redundant. As with any major reference text, it will become outdated, but the core material in each chapter and the avoidance of too much focus on fashion should give the book a reasonable life expectancy. I can only recommend that this is a book that should be in every intensive care unit as a reference book. Its price at £136.00 is, I think, good value.

N. Soni

Effects on the Baby of Maternal Analgesia and Anaesthesia. Edited by F. Reynolds. Published by W. B. Saunders, London. Pp. 282; indexed; illustrated. Price £25.00.

By bringing together evidence from a wide range of sources, this book sets out to answer questions regarding the possible effects that pain relief, anaesthesia during pregnancy and drugs given during lactation may have on mother and child. It is a multi-author book written and edited by recognized experts in the field and covers a wide range of topics relating to the effect of drugs on mother and child. The book has the strengths and weaknesses typical of this type of publication.

The editor has clearly set out to create a reference work where those seeking information on the latest thoughts on many aspects of the use of drugs in anaesthetic practice in the pregnant patient could find a ready source of reference. In this endeavour, the work has largely succeeded. As acknowledged in the preface, such a multi-author book in which each chapter is intended to stand on its own inevitably involves some degree of repetition. This has advantages in that several problems such as the effects of regional anaesthesia on mother and child are approached from different viewpoints, giving a broader spectrum to the problem, although some of the information, particularly that on aorto–caval compression, is simply repeated without advantage. A weakness of the presentation, however, is that individual chapters are inadequately cross-referenced so that a reader studying, for example, the effects of regional anaesthesia on the newborn is not referred to the section on human perinatal pharmacology in which the pharmacology of the local anaesthetics is discussed in some detail. This is unfortunate, as the title of that particular chapter does not give an indication that the pharmacology of the local anaesthetics are dealt with in detail in this section. Nevertheless, the index is generally adequate and the information is readily available.

The book is up to date, with most chapters including references within a year of the publication date.

The first three chapters of the book deal essentially with the basic sciences involved in placental drug transfer, pharmacokinetics in mother and child, and controversies surrounding placental transfer of drugs. This section provides an excellent overview of this complex subject, and is an ideal starting point for anyone wishing to update themselves in the area. The next chapter involves consideration of the effects of regional anaesthesia on placental blood flow and is followed by a chapter on the toxicology of anaesthesia in pregnancy which reviews the morphological teratogenic effects of anaesthetic agents, with the major part of the chapter devoted to the nitrous oxide debate. This is followed logically by an overview of the clinical effects of anaesthesia during pregnancy, which emphasizes the effects that anaesthesia and surgery during pregnancy may have on fetal survival, as opposed to teratogenic effects. The effects of anaesthesia and analgesia on acid–base and respiratory gas exchange in the neonate are dealt with next, with some overlap occurring between this chapter and others concerning aspects of regional anaesthesia. Two chapters cover the effects of anaesthesia and analgesia on stress responses in both mother and child, the latter section being particularly interesting. The following three chapters relate to the effects of opioid and inhalation analgesia, regional analgesia and general anaesthesia on the newborn. The middle of these three contains an overview of the various scoring methods used for assessment of the newborn, which would be particularly useful to a researcher planning a study in this area. The concluding chapter relates to the effects of anaesthesia and analgesia on breast-feeding, with useful references to the transfer of drugs to breast milk.

This book will be an invaluable reference work for the specialist in the field of obstetric anaesthesia. It is not a book for the casual reader, and is generally beyond the level of knowledge required for trainees, but should find a place in departmental libraries of all academic departments with an interest in obstetric anaesthesia. It is an excellent reference source, covering many important topics.

A major weakness of the book from this reviewer's perspective is the virtual absence of detailed discussions on the altered pharmacology of drugs during pregnancy-induced hypertension and the effects that non-anaesthetic agents, particularly vasoactive drugs, sedatives and anti-convulsants administered in the management of this condition may have on mother and child. The only reference to this topic is to the effects of extradural anaesthesia and even this aspect is not covered adequately. The controversy regarding the use of catecholamines is not well considered, nor are the aspects of altered drug metabolism or changes in requirements for fluid loading examined.

This deficit apart, this is a most useful (and reasonably priced) reference work for anyone interested in the pharmacology of anaesthesia and analgesia in relation to the pregnant patient.

M. F. M. James

Percutaneous Local Anaesthesia. By D. Woolfson and D. McCafferty. Published by Ellis Horwood, London. Pp. 270; indexed; illustrated. Price £65.00.

This book reviews the development of local anaesthetic preparations which, when applied to skin, will produce effective analgesia. It is a fascinating account of what is a notable advance in paediatric practice. The authors have been involved in developing effective mixtures.

The book briefly reviews pain mechanisms and local anaesthesia. Two key chapters deal with the percutaneous absorption and the formulation of local anaesthetics for percutaneous delivery. A final chapter describes a variety of clinical uses.

J. Norman

ERRATUM

British Journal of Anaesthesia 1993; 71: 65–76

pp. 70–71: *GABA$_A$ receptor–channels.* "GABA at large concentrations produced a much larger inward current which rapidly desensitized to a sustained concentration" should read "...to a sustained level".

We apologize to the authors for this confusion, which arose during the editorial process.

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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

ASPIRIN-INDUCED ASTHMA

Aspirin and most non-steroidal anti-inflammatory drugs (NSAID) may precipitate acute bronchospasm in some asthmatic subjects [1–3]. This disorder, aspirin-induced asthma (AIA), affects 8–20% of adult asthmatics, and is therefore a common problem [4, 5]. The clinical presentation of this disorder is characteristic [5, 6]. In most patients symptoms do not appear before the third or fourth decade of life, and the problem is rare in asthmatic children. The initial presentation is of an acute episode of vague malaise, sneezing, nasal obstruction and discharge, and often a productive cough. After a few weeks, the initial symptoms resolve, and are replaced by a persistent rhinitis, with the development of nasal polyps. Asthma and aspirin sensitivity then appear in the following months. Ingestion of aspirin by these patients is quickly followed by acute bronchospasm, cutaneous flushing of the head and neck, rhinorrhoea, conjunctival irritation and even circulatory collapse and respiratory arrest. Aspirin may not be recognized as the culprit, as many of the patients may previously have ingested the drug with impunity. This combination of asthma, aspirin intolerance and nasal polyps has been termed the "aspirin triad". In general, the asthma is severe, protracted and difficult to control. Interestingly, there is some evidence that surgical treatment of the nasal polyps may be associated with improvement in the asthma [7].

The problem with AIA for anaesthetists is that there is a marked cross-sensitivity with most other NSAID which may also precipitate severe bronchospasm and other adverse reactions in susceptible individuals [8]. The ability of an NSAID to do this is related directly to the potency of the drug as a cyclo-oxygenase inhibitor [9]. Unfortunately, all the NSAID favoured currently by anaesthetists (including diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac and piroxicam) are extremely potent cyclo-oxygenase inhibitors, and are therefore implicated in this problem. Small doses of most NSAID can rapidly produce bronchospasm in aspirin-sensitive asthmatic patients [2] and may be fatal even after only a single oral dose of an "over-the-counter" preparation [3]. Paradoxically, some NSAID, including sodium salicylate, choline magnesium trisilicate and salicylamide, are well tolerated by aspirin-sensitive asthmatic patients and do not produce bronchospasm, probably because they do not inhibit the cyclo-oxygenase enzyme [10]. Paracetamol is safe for most patients with AIA, although the effect on individual patients should be observed carefully, as some cases of intolerance have been reported [1, 2].

In the absence of reliable *in vitro* tests, diagnosis relies on spirometric studies of the patient when challenged with aspirin. Oral aspirin provocation with incremental doses is used, although challenge by inhalation of metered doses of aerosols containing lysine acetyl salicylate may be preferred. Recently, the measurement of nasal airway resistance after local instillation of aspirin was shown to be a useful and safe test in the diagnosis of this condition [11]. The blood eosinophil count may be increased, but cutaneous tests with aspirin are usually negative. AIA should not be confused with urticaria, with which up to 40% of patients develop weals upon exposure to acetylsalicylate. AIA patients tend also to react adversely to succinate salts, including those of steroid preparations.

The aetiology of AIA has not yet been elucidated fully, although many hypotheses have been proposed. There is little evidence to support an allergic mechanism, as aspirin does not activate mast cells in susceptible individuals [12]. The most convincing explanation is the "cyclo-oxygenase theory" which holds that AIA is caused specifically by pharmacological inhibition by aspirin and most NSAID of arachidonic aid metabolism to prostaglandins by the cyclo-oxygenase enzyme [13]. Analgesics which inhibit cyclo-oxygenase invariably precipitate bronchoconstriction in aspirin-sensitive asthmatics, whereas NSAID devoid of any effect on arachidonic acid metabolism do not produce AIA [10]. There is also a positive correlation between the ability of a drug to inhibit cyclo-oxygenase *in vitro* and propensity to produce AIA in patients [9]. The degree of enzymatic inhibition required to produce bronchoconstriction is individual to each patient, and after the precipitating dose for one drug has been identified, the threshold dose of other drugs can be predicted according to their potency as cyclo-oxygenase inhibitors. In addition, it is possible to desensitize AIA patients to aspirin, and they consequently become tolerant also to other cyclo-oxygenase inhibitors.

Although the importance of cyclo-oxygenase inhibition in the aetiology of AIA is now accepted, it is not clear how the biochemical consequences of this can lead to bronchoconstriction in some asthmatics. Initially it was suggested that asthmatics relied on bronchodilator prostaglandins to maintain airway patency, and that NSAID could produce bronchospasm simply by inhibiting their production, but this view now lacks support. The most popular explanation involves shunting of arachidonic acid metabolism away from prostaglandins to the synthesis of leukotrienes. Arachidonic acid is metabolized either by cyclo-oxygenase to prostaglandins, prostacyclin and thromboxane, or alternatively by lipoxygenase enzymes to leukotrienes, hydroxyeicosatetraenoic acid (HETE) and lipoxins.

Leukotrienes LTB4, LTC4, LTD4 ad LTE4 are products of the 5-lipoxygenase metabolism of arachidonic acid and can produce bronchoconstriction and inflammation of the bronchial mucosa. It is possible that aspirin and the NSAID may precipitate AIA by enhancing the synthesis or action of leukotrienes [5, 14]. AIA could be produced by cyclo-oxygenase inhibitors increasing bronchospastic leukotriene production by diverting arachidonic acid to lipoxygenase pathways, by stimulation of leukotriene synthesis as a result of increased concentrations of HETE, or by loss of compensatory bronchodilator prostaglandins. Indeed, various studies have demonstrated that aspirin increases leukotriene production in aspirin-sensitive asthmatics, but not in aspirin-tolerant asthmatics or normal individuals [15–17]. Yet administration of a leukotriene antagonist only partially inhibits the response of AIA patients to aspirin [18], and the increase in leukotriene production demonstrated after acetylsalicylate administration does not correlate either with the degree of bronchospasm or anti-cyclo-oxygenase activity in susceptible patients [19]. It is unlikely therefore, that direct shunting of arachidonic acid into lipoxygenase pathways is the sole mechanism of AIA, although leukotrienes are obviously involved.

Another hypothesis proposed for AIA is that a chronic viral infection generates bronchial cytotoxic lymphocytes, which are normally suppressed by alveolar macrophage PGE_2, but can be unleashed by cyclo-oxygenase inhibitors, which thus permit the destruction of respiratory tract virus-infected cells [5]. This hypothesis would appear to be consistent with the clinical presentation of AIA, which resembles a viral infection in the early stages, and may explain why only some asthmatics are sensitive to cyclo-oxygenase inhibitors. Recent immunological work has supported an infective cause for AIA, as sufferers have an abnormal distribution of IgG subclasses, indicative of a chronic viral infection [20]. Platelets also have a significant role in AIA, as cyclo-oxygenase inhibitors stimulate them to release cytotoxic mediators in affected individuals [21], and they exhibit abnormal responses *in vitro* to platelet activating factor, collagen and aspirin [22].

What are the practical consequences of AIA for anaesthetists? NSAID have recently been introduced to anaesthetic practice with obvious analgesic benefits, but there are recognized contraindications to their use, including peptic ulceration, bleeding problems and renal impairment. Asthma in adults should be accepted as a relative contraindication, as the NSAID used by anaesthetists are very potent cyclo-oxygenase inhibitors which may precipitate AIA. It should be borne in mind that a reasonable estimate would be that about one in 10 of adult asthmatics will react adversely to aspirin or NSAID, perhaps severely [2], even after one dose [3]. The *British National Formulary* urges caution in the use of cyclo-oxygenase inhibitors in the presence of asthma, and carries a specific warning that any degree of worsening of bronchospasm could be related to the NSAID. Without a doubt, NSAID should be avoided completely in patients with any history at all suggestive of the "aspirin triad" of asthma, nasal polyps and aspirin intolerance, or severe problems will occur [23, 24].

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ORIGINAL ARTICLES

EFFECTS OF INCREASING DOSES OF ALFENTANIL, FENTANYL AND MORPHINE ON MID-LATENCY AUDITORY EVOKED POTENTIALS

D. SCHWENDER, T. RIMKUS, R. HAESSLER, S. KLASING, E. PÖPPEL AND K. PETER

SUMMARY

We have studied dose-dependent effects of alfentanil, fentanyl and morphine on mid-latency auditory evoked potentials (MLAEP). Anaesthesia was induced with alfentanil 100 μg kg^{-1} every 5 min to a total dose of 500 μg kg^{-1} (group I, n = 10), fentanyl 10 μg kg^{-1} every 7 min to a total dose of 50 μg kg^{-1} (group II, n = 10) or morphine 1 mg kg^{-1} for induction and 0.5 mg kg^{-1} every 15 min to a total dose of 3 mg kg^{-1} (group III, n = 10). MLAEP were recorded before and 3–15 min after every opioid dose on vertex (positive) and mastoids on both sides (negative). Latencies of the peaks V, Na, Pa, Nb, P1 (ms) and amplitudes Na/Pa, Pa/Nb and Nb/P1 (μV) were measured. Fast-Fourier transformation was used to calculate power spectra of the AEP. In the awake state, MLAEP had high peak-to-peak amplitudes and a periodic waveform. Power spectra indicated high energy in the 30–40 Hz frequency range. During general anaesthesia with increasing doses of alfentanil, fentanyl and morphine, the brainstem response V was stable. There was a marked increase only in latency and decrease in amplitude of P1. In contrast, for the early cortical potentials Na and Pa, only small increases in latencies and decreases in amplitudes were observed. After the largest doses of alfentanil (500 μg kg^{-1}), fentanyl (50 μg kg^{-1}) and morphine (3 mg kg^{-1}), Na, Pa and Nb showed a similar pattern as in awake patients. In the power spectra, high energy persisted in the 30-Hz frequency range. There were no dose-dependent effects of opioids on MLAEP and no differences between alfentanil, fentanyl, and morphine could be found. (Br. J. Anaesth. 1993; **71**: 622–628)

KEY WORDS

Anaesthesia: general. Analgesics: opioids, fentanyl, alfentanil, morphine. Brain: auditory evoked potential.

The process of transduction, transmission and processing of acoustic stimuli from the cochlea to the cortex can be monitored by the recording of auditory evoked potentials (AEP) [1]. Early components of the AEP (0–10 ms after stimulus) are generated mainly in the brainstem (brainstem auditory evoked potentials—BAEP) and represent the process of stimulus transduction [1]. The mid-latency auditory evoked potentials (MLAEP) occur 10–100 ms after stimulus presentation and are generated by different overlapping areas of the primary auditory cortex. They are the electrophysiological correlate of primary cortical processing of auditory stimuli [1–6]. Finally, late latency auditory evoked potentials (LLAEP) reflect neural activity of the association cortex 100–1000 ms after stimulus onset. They are influenced strongly by processes of stimulus evaluation and cognitive analysis.

The early evoked potentials, generated in the brainstem, remain almost stable under anaesthesia [7–9]. The late cortical components show a great variation of latencies and amplitudes in the awake state [1, 10]. In contrast, mid-latency peaks of the AEP do not differ intra- and interindividually. Recordings of MLAEP therefore offer the opportunity to monitor auditory information processing in the primary auditory cortex during general anaesthesia.

Under general anaesthesia with volatile anaesthetics, MLAEP are suppressed dose-dependently [7, 8, 11], therefore MLAEP have been used to measure depth of anaesthesia and to indicate intraoperative awareness [11, 12]. Opioids produce analgesia and sedation and are also used for induction and maintenance of general anaesthesia. Dose-dependent effects of opioids on MLAEP have not been studied previously. Because intraoperative awareness, and especially the perception of auditory stimuli, are observed occasionally under general anaesthesia with high-dose opioids, we have studied dose-dependent effects of alfentanil, fentanyl and morphine on MLAEP.

PATIENTS AND METHODS

Institutional Ethics Committee approval and informed consent were obtained to study 30 patients (40–70 yr, ASA II and III) undergoing elective

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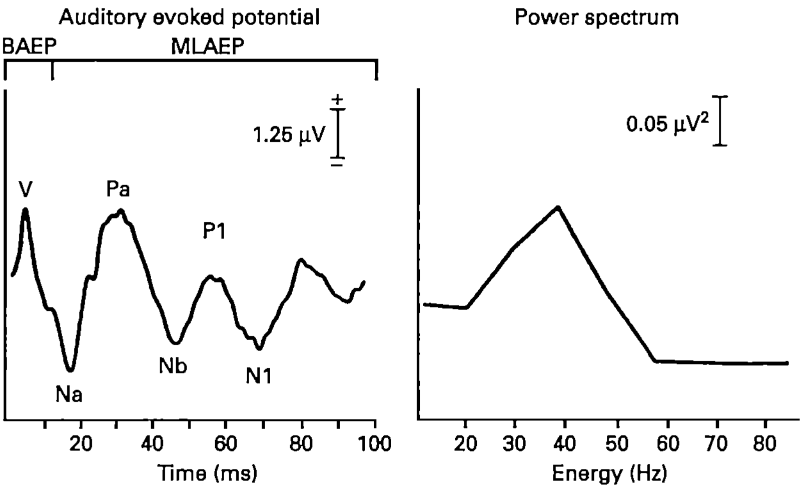


FIG. 1. Auditory evoked potential and its power spectrum of an awake patient. V belongs to the brainstem generated potentials (BAEP), which demonstrates that auditory stimuli were transduced correctly. Na, Pa, Nb and P1 (mid-latency auditory evoked potentials (MLAEP)) are generated in the primary auditory cortex of the temporal lobe and have a characteristic periodic waveform—the power spectrum has its maximal energy in the 30–40 Hz frequency range.

cardiac surgery. After oral premedication with flunitrazepam 1–2 mg 45–60 min before anaesthesia, continuous ECG recordings were commenced and a vein cannulated. The radial artery was cannulated for continuous arterial pressure measurement. Patients were then allocated randomly to one of three groups. Anaesthesia was induced and maintained in group I ($n = 10$) with alfentanil 100 µg kg^{-1} every 5 min to a total dose of 500 µg kg^{-1}, in group II ($n = 10$) with fentanyl 10 µg kg^{-1} every 7 min to a total dose of 50 µg kg^{-1} and in group III ($n = 10$) with morphine 1 mg kg^{-1} for induction and 0.5 mg kg^{-1} every 15 min to a total dose of 3 mg kg^{-1}.

After induction of general anaesthesia with the first opioid injection and loss of consciousness (no response to verbal commands, loss of eye lash reflex), the patient's lungs were ventilated with 100 % oxygen via a face mask. Pancuronium 0.1 mg kg^{-1} was given for neuromuscular block, the trachea was intubated and controlled ventilation with 100 % oxygen commenced. Heart rate (ECG) and direct arterial pressure were recorded continuously and mean arterial pressure was maintained greater than 80 mm Hg. Body core temperature was measured by an oesophageal temperature probe and maintained > 34.5 °C using heated blankets and warmed infusions. A central venous catheter was placed via the internal jugular vein. Controlled ventilation was adjusted to maintain normocapnia (Pa_{CO_2} 4.6–5.9 kPa) and monitored by intermittent arterial blood-gas analysis.

The electrodiagnostic system Pathfinder I (Nicolet Instruments) was used for auditory stimulation, registration and analysis of evoked potentials. Rarefaction clicks of 0.1 ms duration and 70 dB greater than normal hearing level were presented binaurally with a stimulation frequency of 9.3 Hz using acoustically shielded earphones (TDH 39). For recording, silver electrodes were positioned at Cz and A_1/A_2 with Fpz as ground (according to the international 10–20 system). The impedance of all electrodes was maintained less than 0.5 kΩ. An epoch of 100 ms (bin width 0.2 ms) was bandpass filtered (1–1500 Hz) with an analog Butterworth-filter (roll-off 6 dB/Octave) and averaged across 1000 stimulus presentations. The recording procedure was controlled visually on a monitor, and an automatic artefact detector rejected signals greater than 96 % of full scale. To guarantee reliability of the signal and correct transmission and transduction of the auditory stimuli, evoked potentials without a brainstem response (peak V) were rejected also.

Latencies of the peaks V, Na, Pa, Nb and P1 (ms) and amplitudes Na/Pa, Pa/Nb and Nb/P1 (µV) were measured. For frequency analysis, a Fast-Fourier Transformation was used to calculate power spectra of the AEP. For each situation, AEP of each individual patient and an interindividual grand average calculated from the individual AEP of all patients in each group were analysed. Auditory evoked potentials were recorded awake and 3–5 min after every injection of alfentanil, 5–7 min after every fentanyl injection and 13–15 min after every injection of morphine. One AEP averaged from 1000 responses with a stimulation rate of 9.3 represented approximately a 2-min period.

Statistical analysis. For the peak latencies V, Na, Pa, Nb and P1 and amplitudes Na/Pa, Pa/Nb and Nb/P1, the Wilcoxon test was used within groups and the Kruskal–Wallis test between groups. $P < 0.05$ was considered statistically significant. Statistical analysis included Bonferroni's correction (α-adjustment).

RESULTS

Figure 1 shows an original tracing of an auditory evoked potential (left side) and its power spectrum (right side) of an awake patient. V belongs to the brainstem-generated potentials (BAEP), which demonstrates that auditory stimuli were correctly transduced [1]. Na, Pa, Nb, P1 (MLAEP) are generated in the primary auditory cortex of the temporal lobe [1–6]; they are the electrophysiological correlate of the primary cortical processing of the

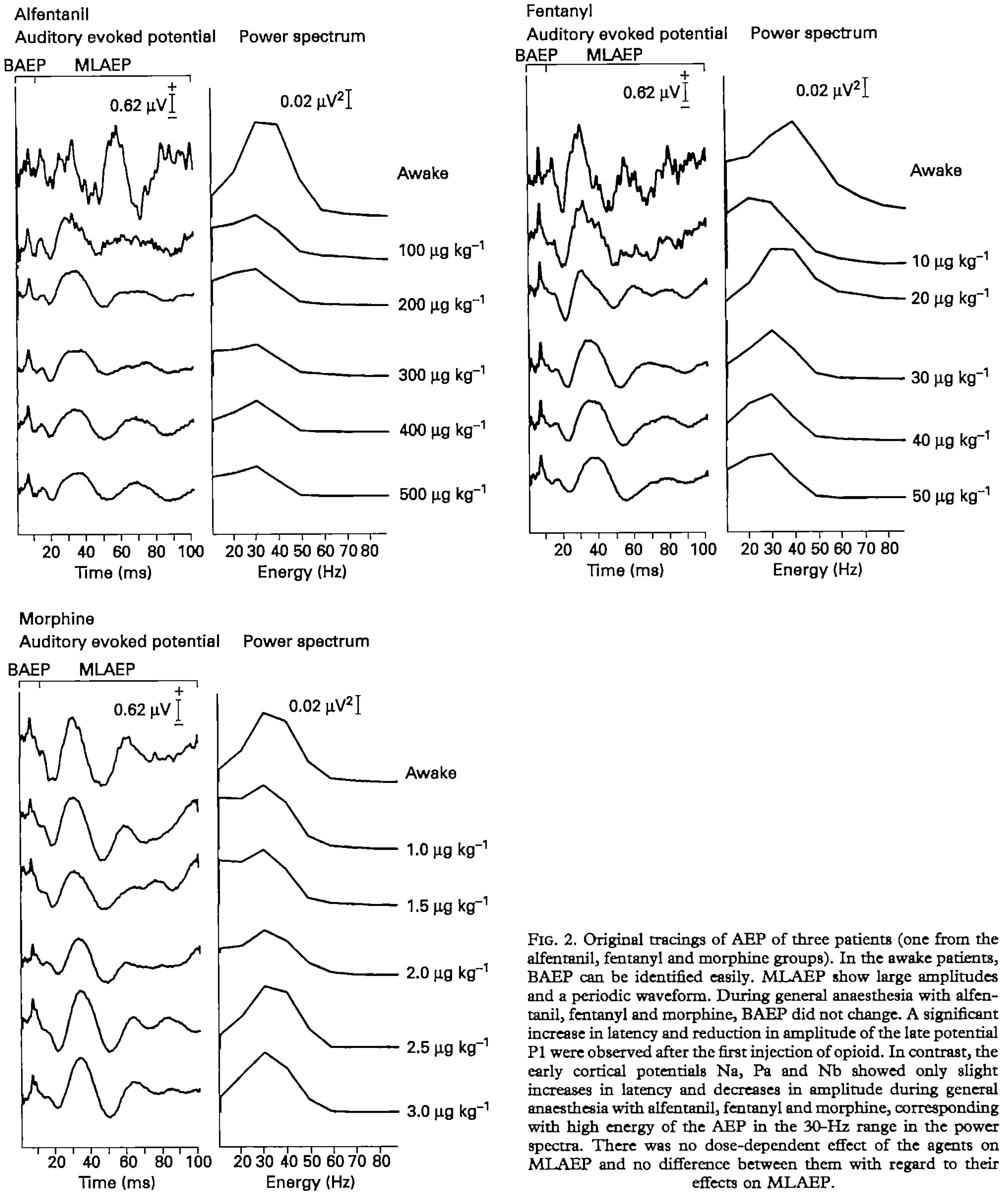
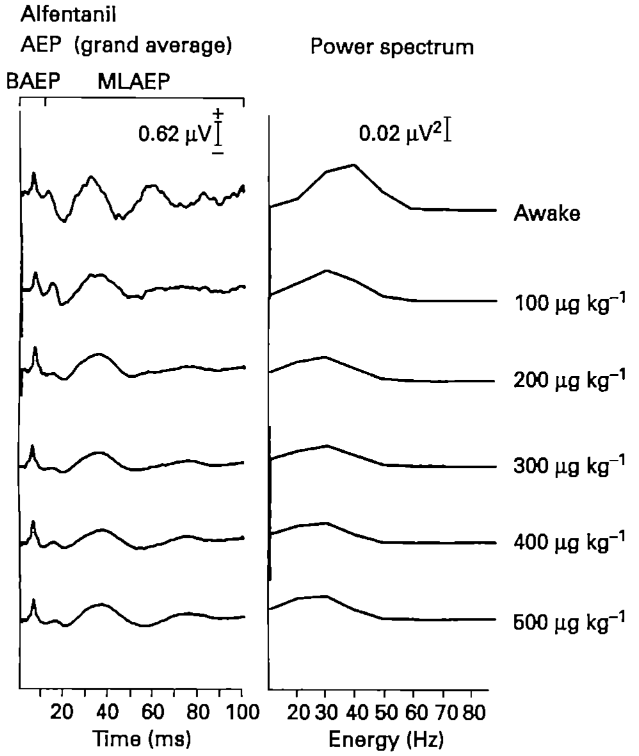
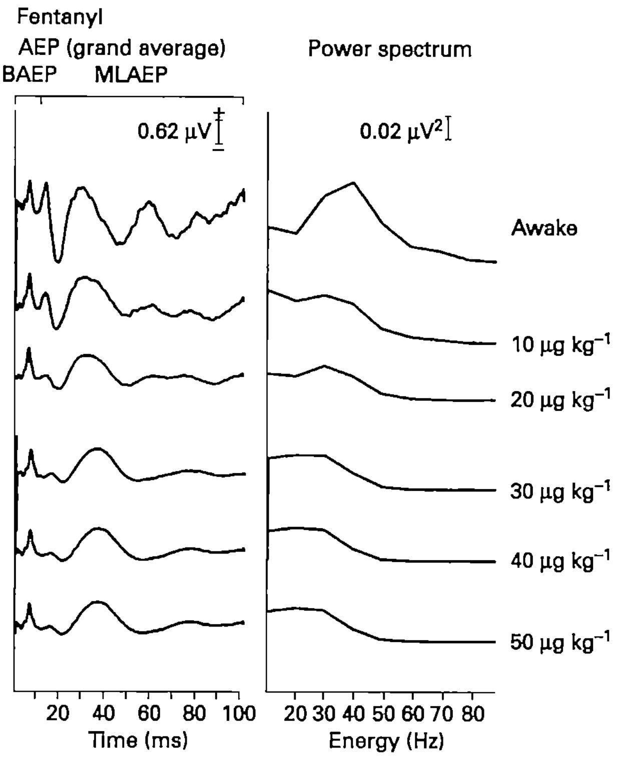


FIG. 2. Original tracings of AEP of three patients (one from the alfentanil, fentanyl and morphine groups). In the awake patients, BAEP can be identified easily. MLAEP show large amplitudes and a periodic waveform. During general anaesthesia with alfentanil, fentanyl and morphine, BAEP did not change. A significant increase in latency and reduction in amplitude of the late potential P1 were observed after the first injection of opioid. In contrast, the early cortical potentials Na, Pa and Nb showed only slight increases in latency and decreases in amplitude during general anaesthesia with alfentanil, fentanyl and morphine, corresponding with high energy of the AEP in the 30-Hz range in the power spectra. There was no dose-dependent effect of the agents on MLAEP and no difference between them with regard to their effects on MLAEP.

auditory stimuli and have a characteristic periodic waveform—the power spectrum has its maximal energy in the 30–40 Hz frequency range.

Original tracings of AEP from three patients (one from the alfentanil, fentanyl and morphine groups) are shown in figure 2. The upper traces show the AEP of the awake patients. BAEP can be identified easily; MLAEP show large amplitudes and a periodic waveform. AEP of the awake patients have their maximal energy within the 30–40 Hz frequency range. During general anaesthesia with alfentanil, fentanyl and morphine, BAEP did not change. They are identical with those recorded in the awake state. With increasing doses of alfentanil, fentanyl and morphine, significant latency increase and amplitude reduction of the late potential P1 may be observed. This effect occurred after the first opioid injection. Additional doses of opioids caused no further reduction of P1 amplitude. In contrast, the early cortical potentials Na, Pa and Nb showed only slight





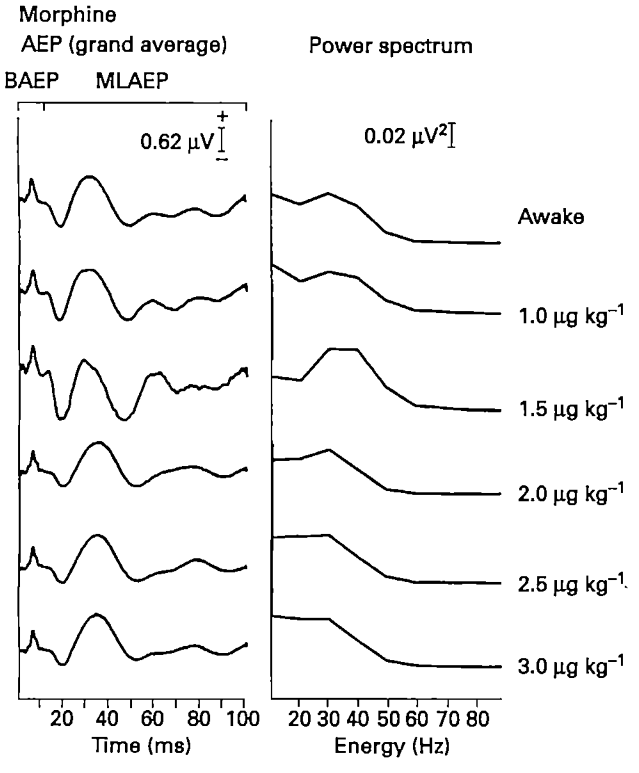


FIG. 3. Interindividual grand averages of the individual AEP with alfentanil, fentanyl or morphine anaesthesia. AEP of the awake patients showed high peak-to-peak amplitudes and a periodic wave form. After the first opioid injection, P1 showed a significant increase in latency and decrease in amplitude. In contrast, BAEP and the early cortical potentials Na, Pa and Nb changed only slightly compared with the awake state.

increases in latencies and decreases in amplitudes during general anaesthesia with alfentanil, fentanyl and morphine. They showed a pattern similar to those recorded in the awake state, corresponding with AEP high energy in the 30-Hz range of the power spectra. There was no dose-dependent effect of alfentanil, fentanyl and morphine on MLAEP and no difference between alfentanil, fentanyl and morphine in their effects on MLAEP.

The same pattern was seen in the interindividual grand averages of the individual AEP with alfentanil, fentanyl and morphine (fig. 3). The high average rate, an increased signal-to-noise ratio and inter-individual differences, especially in the late latency range (P1), led to a slight flattening of the potential. Again, AEP of awake patients showed large peak-to-peak amplitudes and a periodic wave form. After the first injection of opioid, P1 showed a significant increase in latency and decease in amplitude. In contrast, BAEP and the early cortical potentials Na,

TABLE I. *Mean* (SD) *latencies of V, Na, Pa, Nb and P1, and amplitudes Na/Pa, Pa/Nb and Nb/P1 for the three groups and measurements 1–6.* * $P < 0.05$ *compared with measurement 1* (*awake*)

	Alfentanil group	Fentanyl group	Morphine group
V (ms)			
1	6.43 (0.45)	6.38 (0.35)	6.20 (0.35)
2	6.48 (0.65)	6.38 (0.33)	6.25 (0.39)
3	6.46 (0.46)	6.34 (0.34)	6.29 (0.36)
4	6.53 (0.61)	6.32 (0.39)	6.44 (0.61)
5	6.34 (0.27)	6.34 (0.43)	6.38 (0.36)
6	6.42 (0.30)	6.38 (0.44)	6.42 (0.36)
Na (ms)			
1	20.02 (1.41)	18.82 (0.76)	19.04 (1.13)
2	20.08 (1.93)	18.70 (1.75)	18.73 (0.90)
3	21.02 (3.22)	19.50 (1.16)	19.29 (2.16)
4	20.80 (2.04)	20.38 (1.19)	19.50 (1.27)
5	21.30 (1.90)	20.50 (1.09)	20.38 (2.85)
6	21.34 (1.96)	21.46 (1.30)	21.40 (2.86)
Pa (ms)			
1	32.23 (2.28)	30.87 (2.15)	30.69 (1.63)
2	34.69 (2.31)*	32.69 (1.90)	31.05 (0.86)
3	36.09 (4.71)*	33.18 (1.91)	32.44 (1.62)*
4	35.84 (2.18)*	35.24 (0.95)*	35.05 (1.50)*
5	36.40 (3.32)*	37.42 (2.01)*	35.20 (2.93)*
6	37.48 (2.89)*	37.04 (2.59)*	35.92 (1.48)*
Nb (ms)			
1	47.08 (3.22)	47.48 (2.53)	46.69 (2.27)
2	54.78 (6.78)*	54.32 (8.24)	49.09 (3.91)
3	59.66 (11.11)*	53.18 (5.47)	49.92 (3.64)*
4	58.10 (4.75)*	60.56 (9.14)*	54.64 (6.34)*
5	60.20 (6.86)*	63.16 (9.78)*	56.69 (7.25)*
6	60.20 (3.35)*	65.66 (13.06)*	57.26 (7.99)*
P1 (ms)			
1	62.65 (5.07)	60.52 (1.92)	61.11 (4.00)
2	74.58 (11.40)*	70.66 (13.09)*	63.11 (7.68)
3	77.38 (12.87)*	74.60 (11.92)*	66.67 (9.89)*
4	76.68 (6.89)*	80.48 (9.81)*	71.69 (9.61)*
5	80.73 (10.69)*	83.44 (11.04)*	75.31 (10.53)*
6	78.36 (7.98)*	84.96 (11.44)*	76.24 (10.67)*
Na/Pa (μV)			
1	1.16 (0.43)	1.45 (0.54)	1.32 (0.33)
2	0.95 (0.49)	1.29 (0.41)	1.05 (0.34)
3	0.70 (0.39)	1.04 (0.38)	1.13 (0.43)
4	0.76 (0.37)	1.03 (0.34)	1.22 (0.50)
5	0.63 (0.30)	0.97 (0.28)	1.17 (0.49)
6	0.74 (0.23)	0.83 (0.37)	1.06 (0.46)
Pa/Nb (μV)			
1	1.22 (0.58)	1.51 (1.04)	1.48 (0.58)
2	0.96 (0.59)	1.38 (1.15)	1.23 (0.49)
3	0.84 (0.61)	1.41 (1.19)	1.33 (0.44)
4	0.85 (0.57)	1.30 (0.74)	1.39 (0.63)
5	0.91 (0.55)	1.13 (0.58)	1.43 (0.54)
6	0.95 (0.29)	1.15 (0.76)	1.31 (0.55)
Nb/P1 (μV)			
1	1.15 (0.65)	1.24 (0.77)	1.21 (1.06)
2	0.50 (0.42)*	0.50 (0.56)*	0.50 (0.45)*
3	0.29 (0.26)*	0.39 (0.26)*	0.39 (0.29)*
4	0.24 (0.25)*	0.39 (0.24)*	0.50 (0.26)*
5	0.44 (0.40)*	0.39 (0.23)*	0.64 (0.24)*
6	0.35 (0.28)*	0.32 (0.20)*	0.67 (0.40)*

Pa and Nb changed only slightly compared with the awake state; even after the largest doses of alfentanil, fentanyl and morphine, they could be recorded and identified.

Mean (SD) values of the latencies of V, Na, Pa, Nb and P1, and amplitudes Na/Pa, Pa/Nb and Nb/P1 for the three groups and the six measurement points are shown in table I. The awake values of the electrophysiological data are within the normal range. During general anaesthesia with alfentanil, fentanyl and morphine, a marked and statistically significant increase in latencies of Nb and P1 occurred. This effect was seen after the first or second injection of alfentanil, fentanyl or morphine and remained stable with increasing administration of opioid. In contrast, BAEP did not increase and the early cortical potentials Na and Pa increased only slightly with increasing doses of alfentanil, fentanyl and morphine. Nevertheless, this reached statistical significance between the awake value and Pa measurements 2–6 in the alfentanil group, Pa measurements 4–6 in the fentanyl group and Pa measurements 3–6 in the morphine group. The amplitude Nb/P1 was reduced significantly after the first opioid injection and remained reduced with increasing doses of alfentanil, fentanyl or morphine. In contrast, for the amplitudes Na/Pa and Pa/Nb there was only a slight, statistically insignificant reduction. No dose-related effects of alfentanil, fentanyl or morphine on MLAEP peak latencies and amplitudes were observed and there were no differences between alfentanil, fentanyl and morphine in their effects on MLAEP.

DISCUSSION

Latencies of peaks V, Na, Pa, Nb, P1 and N1 showed small SD and corresponded well with peak latencies obtained under experimental conditions [1, 13]. Relative amplitudes of the components Na/Pa, Pa/Nb and Nb/P1 were within the normal range also and showed a greater interindividual variability than latencies.

The influence of the volatile anaesthetics isoflurane, enflurane and halothane on MLAEP has been investigated [7, 8, 14, 15]. With volatile anaesthetics, brainstem components of the auditory evoked potential are prolonged only slightly in latency. In contrast, mid-latency components show typically a dose-dependent increase in latencies and a decrease in amplitudes. At about 1 MAC isoflurane, MLAEP components are suppressed almost completely [7]. Initial transduction of auditory stimuli remains intact and auditory stimuli can be processed up to a brainstem or mid-brain level. In contrast, processing of auditory stimuli is blocked at the level of the primary auditory cortex.

Results obtained from sensory evoked potentials recorded in other modalities under volatile anaesthetics are in accordance with these findings. The early and late cortical components of visual and somatosensory evoked potentials are suppressed during anaesthesia with isoflurane, enflurane and halothane [16–23]. These studies demonstrate that volatile anaesthetic agents induce a general suppression of the afferent stimulus conduction and processing within the different sensory channels in the central nervous system. One possible explanation for the general suppression of cortical components in evoked potentials might be that volatile anaesthetics affect many different excitable biological membranes in the human cortex. Interaction between volatile anaesthetics and the phospholipid bilayers of the neural membrane blocking stimulus processing has been proposed [24].

The effects of opioids on MLAEP differ: there was no or only a slight increase in the latencies of Na and Pa and a slight decrease in their amplitudes. Only Nb and P1 latencies increased and P1 amplitude decreased significantly after the first or second injection of opioid. In contrast, BAEP and the early cortical peaks Na and Pa remained stable or changed only slightly, even after the largest opioid doses (alfentanil 500 $\mu g\ kg^{-1}$, fentanyl 50 $\mu g\ kg^{-1}$, morphine 3 $mg\ kg^{-1}$). They are similar to those in the awake state. There were no dose dependent effects of opioids on MLAEP and no differences between alfentanil, fentanyl and morphine with regard to their effects. Because Na, Pa and Nb are generated in the primary auditory cortex of the temporal lobe [1–6], auditory stimuli may be processed, at least partly, in the primary auditory cortex in the presence of high-dose opioids.

It is important to note that only the late latency of P1 increased and its amplitude decreased significantly with the opioids. This effect was the same for alfentanil, fentanyl and morphine. This phenomenon was observed after induction of general anaesthesia with the first bolus injection of opioid and the patient's loss of consciousness. Animal studies, and studies in humans, provide evidence for a functional interdependence between the wake–sleep rhythm, the activity of the ascending reticular activating system and the P1 amplitude [25, 26]. Most probably, P1 is generated by mesencephalic structures, the cholinergic cells of the pedunculopontine tegmental nucleus [27, 28]. They provide input to ascending projection pathways to thalamic nuclei. These are part of the ascending reticular activating system and are involved directly in wake–sleep behaviour. A significant reduction in P1 amplitude can be observed during natural sleep, especially during slow-wave sleep. It is reversible during rapid eye movement sleep episodes. Furthermore, the P1 amplitude can be correlated with the different sleep stages defined by EEG brain activity [25, 26]. Therefore, P1 amplitude changes were interpreted as an electrophysiological correlate of changes in vigilance and changes of the tonic activity of the ascending reticular activating system.

Neurophysiological investigations provide evidence that the ability to perceive and process auditory stimuli is preserved even in states of reduced vigilance. Furthermore, many studies indicate that, during states of reduced awareness, auditory information can be stored in the memory and recalled afterwards by non-conscious implicit memory function without any knowledge of the circumstances under which the individual gained that information [29, 30]. The likelihood of information being processed and recalled depends on the personal and emotional relevance of the auditory message.

The pattern of MLAEP changes with high-dose opioids seemed to be similar to that recorded during natural sleep. With opioids, there was only a slight slowing of cortical stimulus transmission and cortical stimulus processing in the auditory modality. In contrast with volatile anaesthetics (halothane, enflurane, isoflurane), opioids cannot suppress auditory stimulus processing in the primary auditory cortex completely and in a dose dependent fashion—processing of auditory stimuli in the primary auditory cortex remains intact to some extent.

Kileny, Dobson and Gelfand [31] investigated the effect of hypothermia on auditory evoked potentials during cardiac surgery. They showed that increasing hypothermia and reduced perfusion pressure induced prolongation of peak latencies of MLAEP, whereas high-dose opioid analgesia did not change MLAEP or brainstem-generated potentials [31, 32]. In accordance with these results, early cortical components of somatosensory and visual evoked potentials remain stable under opioids [18, 19, 21, 33, 34]. Furthermore, an auditory evoked steady state response (ASSR), which can be recorded in the processed EEG, seems to be correlated with adequate sensory information processing and the state of consciousness. The ASSR is suppressed under 1 MAC of volatile anaesthetics. In contrast, under opioids the ASSR is affected only slightly [35, 36]. This is a further indication that opioids may suppress sensory information processing and consciousness less reliably than volatile anaesthetics.

Opioid receptors are located in the dorsal horn of the spinal cord, the periaqueductal grey, the raphe nuclei, the medulla oblongata, the thalamus and the limbic system. They have analgesic, sedative, antitussive and ventilatory depressant effects. The μ receptor mediates analgesia, change of emotional state and vigilance in the sense of euphoria and sedation by inhibiting the afferent input to the limbic system [37]. General suppression of the classical non-nociceptive sensory pathways, as achieved with volatile anaesthetics, cannot be documented with opioids. This corresponds well with clinical reports of intraoperative awareness and perception of auditory stimuli if opioids only are used during general anaesthesia [38–46]. Opioids, even in very large doses, do not always provide a reliable suppression of auditory stimulus processing during anaesthesia. Our data indicate that volatile agents (enflurane or isoflurane) provide a more reliable suppression of auditory stimulus perception and processing, and probably intraoperative awareness, compared with high-dose opioids.

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MID-LATENCY AUDITORY EVOKED POTENTIALS DURING KETAMINE ANAESTHESIA IN HUMANS

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SUMMARY

We studied mid-latency auditory evoked potentials (MLAEP) during induction of general anaesthesia with ketamine 2 mg kg^{-1}. MLAEP were recorded before, during and after induction of general anaesthesia on the vertex (positive) and mastoid (negative) positions. Latencies of the peak V, Na, Pa, Nb, P1 and amplitudes Na/Pa, Pa/Nb and Nb/P1 were measured. Fast-Fourier transformation was used to calculate power spectra of the MLAEP. In the awake state, MLAEP had large peak-to-peak amplitudes and a periodic waveform. Peak latencies remained within the normal range. Power spectra indicated high energy in the 30–40 Hz frequency range. After induction of general anaesthesia with ketamine, there was no change in latency of peaks V, Na, Pa, Nb, P1 and no apparent reduction in amplitudes Na/Pa, Pa/Nb and Nb/P1. In the power spectra, frequencies in the range of 30–40 Hz retained high energy. Amplitudes and latencies of MLAEP did not change during induction of general anaesthesia with ketamine. Primary processing of auditory stimuli in the primary auditory cortex seemed to be preserved under ketamine. Suppression of sensory (auditory) information processing must take place at a higher cortical level in a dissociative manner. (Br. J. Anaesth. 1993; **71**: 629–632)

KEY WORDS

Anaesthesia, general: ketamine, auditory evoked potential.

In an accompanying paper, we have described the use of mid-latency peaks of the auditory evoked potential (MLAEP) to assess depth of anaesthesia with opioids, and reviewed the data with volatile anaesthetic agents [1]. The anaesthetic state under ketamine differs from that produced by volatile anaesthetic agents [2]. Dreams and hallucinations are well known phenomena associated with ketamine [3] and may be related to insufficient suppression of sensory stimulus processing. The effect of ketamine on MLAEP, indicating primary cortical processing of auditory stimuli, has not been studied. Therefore, we investigated changes in MLAEP during induction of general anaesthesia with ketamine.

PATIENTS AND METHODS

Institutional Ethics Committee approval and informed consent were obtained to study 20 patients (ASA I and II, ages 20–50 yr) undergoing elective minor gynecological or urological surgery. After oral premedication with flunitrazepam 1–2 mg, 45–60 min before anaesthesia, continuous ECG recordings were commenced, a vein was cannulated and a pneumatic device was attached to the patient to obtain automatic oscillatory arterial pressure measurements every 1 min. General anaesthesia was induced with ketamine 2 mg kg^{-1} i.v. After loss of consciousness (no response to verbal commands, loss of eye lash reflex), the patient's lungs were ventilated with 100% oxygen via a face mask. Vecuronium 0.1 mg kg^{-1} was given, the trachea was intubated and controlled ventilation with 100% oxygen commenced.

The electrodiagnostic system Pathfinder I (Nicolet Instruments) was used for auditory stimulation, registration and analysis of evoked potentials, as described in the accompanying paper [1]. Auditory evoked potentials were recorded awake and on line with the start of the ketamine injection until 6 min after the ketamine injection. One AEP averaged out of 1000 responses with a stimulation rate of 9.3 represented approximately a 2-min period: AEP 1 = awake; AEP 2 = 0–2 min; AEP 3 = 2–4 min; AEP 4 = 4–6 min after ketamine injection. For every situation, one interindividual grand average was calculated from the individual AEP.

For statistical comparison of the peak latencies V, Na, Pa, Nb, P1 and the peak amplitudes Na/Pa, Pa/Nb and Nb/P1, the Wilcoxon test was used. $P < 0.05$ was considered statistically significant. Statistical analysis included Bonferroni's correction (α-adjustment).

RESULTS

Original tracings of AEP of four patients are shown in figure 1. Data are shown from the awake patients and 0–2 min, 2–4 min and 4–6 min after ketamine injection. Upper traces display the AEP of the awake patient. BAEP can be identified easily. MLAEP show large amplitudes and a characteristic periodic waveform. During general anaesthesia, BAEP and MLAEP can be identified as in the awake state. There was no change in latency and amplitudes of

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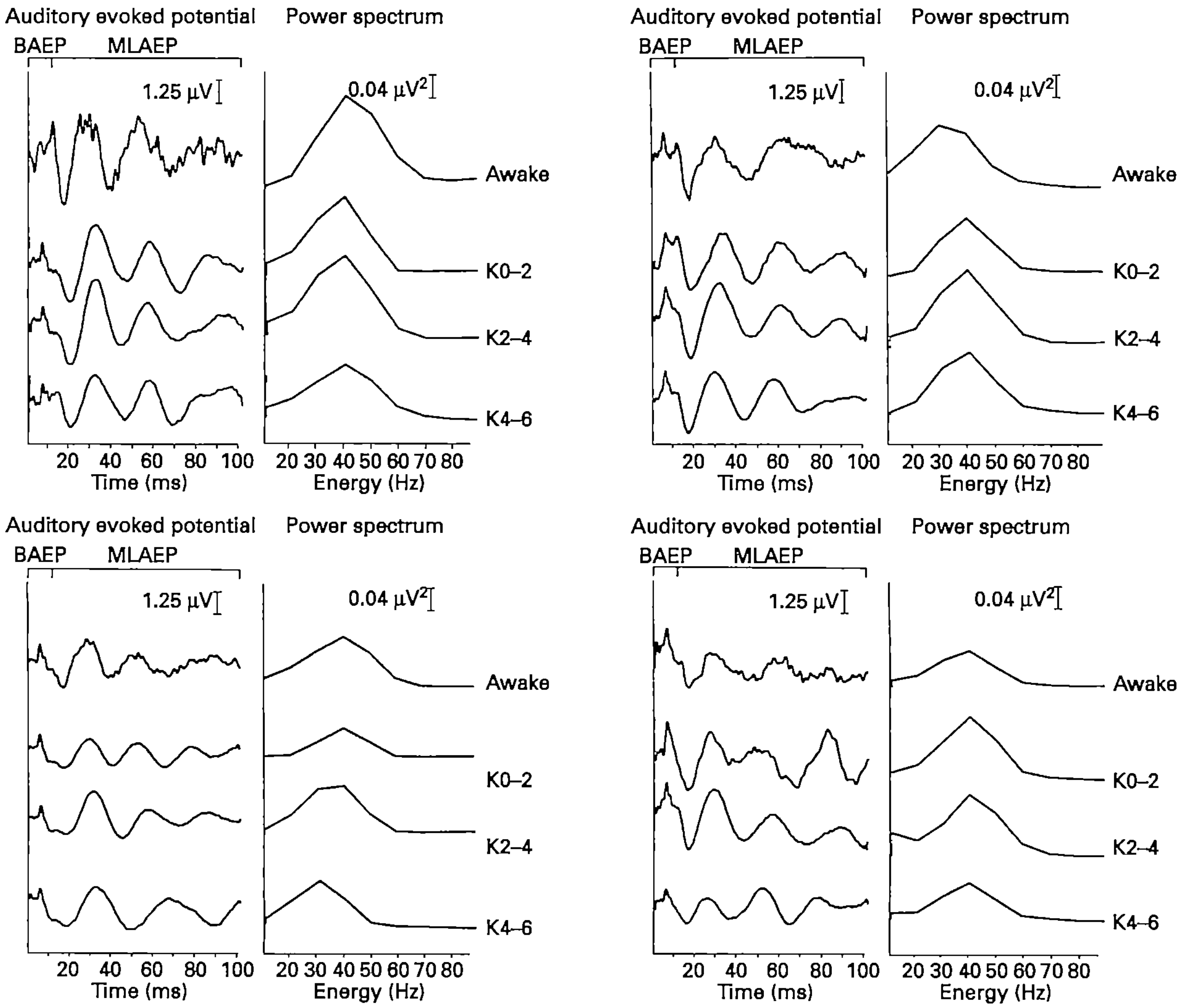

FIG. 1. Original tracings of AEP of four patients under ketamine. Data are shown from the awake patients and 0–2 min, 2–4 min and 4–6 min after ketamine injection. In every upper trace the AEP of the awake patients can be seen. BAEP can be identified easily. MLAEP show large amplitudes and a characteristic periodic waveform. During general anaesthesia BAEP and MLAEP can be identified, as in the awake state. There is no change of latencies and amplitudes of the peaks V, Na, Pa, Nb and P1 compared with the awake state.

the peaks V, Na, Pa, Nb and P1 compared with the awake state. The only difference between the AEP awake (AEP 1 and 2) and the AEP during anaesthesia (AEP 3 and 4) was a decreased high frequency muscle artefact during anaesthesia because of the use of a neuromuscular blocking drug.

The same results were obtained in the inter-individual grand average of the 20 individual AEP (fig. 2). MLAEP of the awake patients had large peak-to-peak amplitudes and a periodic waveform. During anaesthesia with ketamine there was no increase in MLAEP peak latencies or decrease in MLAEP peak amplitudes; MLAEP showed exactly the same pattern as those of awake patients, indicating that the electrophysiological condition of primary stimulus processing in the primary sensory cortex is preserved under ketamine anaesthesia.

Mean (SD) latencies of the peaks V, Na, Pa, Nb, P1 and amplitudes Na/Pa, Pa/Nb and Nb/P1 for the patients when awake, 0–2 min, 2–4 min and 4–6 min after ketamine injection are presented in table I. In the awake state, mean latencies of peaks V (5.84 (0.31) ms), Na (18.6 (2.31) ms), Pa (30.4 (3.14) ms), Nb (47.5 (8.23) ms) and P1 (66.8 (13.2) ms) and relative amplitudes of Na/Pa (1.64 (0.73) µV), Pa/Nb (1.05 (0.67) µV) and Nb/P1 (0.76 (0.47) µV) were within the normal range. During general anaesthesia with ketamine, there was no significant increase in the latencies of V, Na, Pa, Nb, P1 and no decrease in the amplitudes Na/Pa, Pa/Nb and Nb/P1 compared with the awake state. With ketamine all features of the MLAEP corresponded to the preanaesthetic values of the awake patients.

DISCUSSION

With volatile anaesthetics, brainstem components of the auditory evoked potential are prolonged in latency only slightly. In contrast, mid-latency components show typically a dose-dependent increase in latencies and a decrease in amplitudes. At approximately 1 MAC isoflurane, MLAEP components are suppressed almost completely [4]. Initial transduction of auditory stimuli remains intact and auditory stimuli can be processed up to a brainstem or midbrain level. In contrast, processing of auditory stimuli is blocked at the level of the primary auditory cortex.

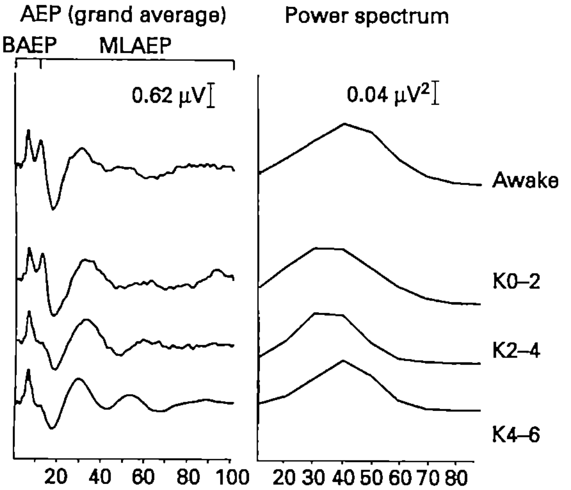

FIG. 2. Interindividual grand averages of the 20 individual AEP. The MLAEP of the awake patients have large peak-to-peak amplitudes and a periodic waveform. During anaesthesia with ketamine there was no increase in MLAEP peak latencies or decrease in MLAEP peak amplitudes.

In contrast to these volatile anaesthetics, ketamine apparently had a different effect on MLAEP. An induction dose of ketamine did not suppress mid-latency components. Peak latencies and amplitudes did not change compared with MLAEP in the awake state. Several investigators have demonstrated that the generators of the MLAEP are localized in the primary auditory cortex of the temporal lobe [5–10]. This indicates that an induction dose of ketamine did not suppress auditory stimulus processing in the primary sensory cortex. The effect of larger doses of ketamine on MLAEP has not been investigated and further studies are required to elucidate dose-dependent effects.

Spontaneous EEG and processed EEG (median and spectral edge frequency) can be suppressed with ketamine and especially with S(+)ketamine (one of the two optical isomers of racemic ketamine), but R(−)ketamine has little effect on general EEG activity [11, 12]. These findings cannot be transferred to the recording of stimulus-evoked EEG signals such as auditory evoked potentials. In contrast, our results demonstrate that, with ketamine, the primary processing of sensory stimuli in the primary sensory cortex remained unchanged, although global cortical activity may be reduced, as demonstrated by EEG studies. A dose-dependent block of primary auditory stimulus processing, as shown for volatile anaesthetic agents, cannot be achieved with an induction dose of ketamine. Thus a disruption of sensory processing or a disconnection of processed information from conscious representation may occur at a higher cortical level.

One question based upon these findings is if intact stimulus processing, as demonstrated with evoked potentials, is required in order to allow higher cortical stimulus processing (stimulus evaluation) during general anaesthesia. The relation between MLAEP and conscious awareness, explicit conscious recall and response to verbal commands in surgical patients and anaesthetized volunteers during different sub-MAC concentrations of nitrous oxide and isoflurane have been investigated [13, 14]. When MLAEP peak latencies were increased significantly compared with the awake state, no conscious awareness, recall or response to verbal commands were observed. In contrast, when MLAEP were increased only slightly during anaesthesia, a high incidence of arousal was found. The AEP variables were related significantly to the level of response and fitted the response more closely than end-expiratory gas concentrations. Furthermore, it has been shown that the preserved MLAEP during general anaesthesia correlates with intraoperative motor signs of wakefulness [14–16]. In patients undergoing Caesarean section, MLAEP indicated periods of intraoperative consciousness and correlated well with the post-operative recall of surgical manipulations [17]. It has been shown also that, during phases of intact MLAEP during cardiac surgery, acoustic information presented during operation can be perceived and remembered implicitly in a postoperative interview [18]. Therefore, normal MLAEP with ketamine anaesthesia indicate that perception of auditory information may not be suppressed completely.

Investigations with ketamine and evoked potentials of other sensory modalities indicate that the cortical excitability in the primary sensory cortices remains unimpaired under ketamine anaesthesia. For example, ketamine had no effect on intracerebral recordings of visual evoked potentials in the primary visual cortex of Rhesus monkeys [19]. In contrast, visual evoked potentials recorded in the extrastriate visual cortex were suppressed significantly. These

TABLE I. *Mean (SD) latencies of the peaks V, Na, Pa, Nb, P1 and amplitudes Na/Pa, Pa/Nb and Nb/P1 for the patients awake, 0–2 min, 2–4 min and 4–6 min after ketamine injection. During general anaesthesia with ketamine there was no statistically significant increase in latencies of V, Na, Pa, Nb, P1 and no decrease in amplitudes Na/Pa, Pa/Nb and Nb/P1 compared with the awake state*

		Ketamine		
	Awake	0–2 min	2–4 min	4–6 min
V (ms)	5.84 (0.31)	5.85 (0.24)	5.88 (0.25)	5.92 (0.26)
Na (ms)	18.6 (2.31)	18.3 (2.29)	17.8 (1.29)	19.0 (2.06)
Pa (ms)	30.4 (3.14)	32.1 (3.51)	31.5 (5.28)	32.9 (4.18)
Nb (ms)	47.5 (8.23)	49.9 (7.63)	48.1 (9.49)	48.7 (8.04)
P1 (ms)	66.8 (13.2)	65.6 (11.2)	61.1 (11.9)	61.6 (10.3)
Na/Pa (µV)	1.64 (0.73)	1.52 (0.70)	1.39 (0.73)	1.29 (0.54)
Pa/Nb (µV)	1.05 (0.67)	1.38 (0.84)	1.35 (0.76)	1.17 (0.68)
Nb/P1 (µV)	0.76 (0.47)	1.07 (0.81)	1.15 (1.09)	0.96 (0.87)

findings confirm also the dissociation between stimulus registration and processing in the primary sensory cortex and stimulus evaluation represented by higher cortical areas. Similarly, results obtained in the somatosensory modality demonstrate impaired stimulus evaluation by higher cortical areas. Potentials evoked by nociceptive stimuli are suppressed in the reticular formation of the midbrain and in the medial nuclei of the thalamus after injection of ketamine [20]. Besides the suppression of evoked responses in these areas, spontaneous neuronal activity is reduced also [21]. This leads to the conclusion that ketamine disturbs the processing and evaluation of the nociceptive stimuli in the reticular formation.

From a theoretical, neurophysiological point of view the present study, and data described in the literature, indicate that ketamine does not induce a general suppression of the perception and processing of sensory stimuli. Therefore, one might speculate on whether or not the anaesthetic effect of ketamine relies on a disturbed stimulus evaluation in secondary associative cortices. Sensory stimuli without any nociceptive character are transmitted up to primary sensory cortices under ketamine anaesthesia. These observations may support the concept of dissociative anaesthesia under ketamine—that is, a dissociation of perception and primary processing in the primary sensory cortices and secondary evaluation of sensory stimuli. According to this concept, ketamine allows primary sensory stimulus processing while nociception is blocked. The clinical observation of a high incidence of dreams and hallucinations during general anaesthesia with ketamine may be interpreted as inadequate suppression of sensory stimulus processing, or even consciousness.

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A MEASURE OF CONSCIOUSNESS AND MEMORY DURING ISOFLURANE ADMINISTRATION: THE COHERENT FREQUENCY†

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SUMMARY

The coherent frequency (CF) of the auditory evoked response (AER) is derived using auditory clicks presented at frequencies in the range 5–47 Hz. CF and psychological performance were measured while seven subjects breathed isoflurane in doses increasing from 0% to 0.2%, 0.4% and 0.8% end-tidal concentration and then decreasing to 0%. With increasing doses of isoflurane, CF decreased and there was a decrease in within-list recognition (WLR) and category recognition (CR) scores. There was a correlation between changes in CF and WLR ($P < 0.05$) and between CF and category recognition (CR) ($P < 0.05$). A painful stimulus given in conjunction with 0.4% isoflurane caused an increase in CF, WLR and CR in some subjects. This did not reach statistical significance for the group as a whole, apart from the short word interval scores in the WLR which indicated an increase in attention ($P < 0.01$). Subjects did not respond with 0.8% isoflurane, either before or after painful stimulation. Reduction of end-tidal isoflurane from 0.8% to 0% caused an increase in the CF and improved performance on the psychological tests. A category generation task on recovery showed no evidence of implicit learning of words presented in conjunction with 0.8% isoflurane. Memory testing after the trial showed a relationship between the CF obtained with isoflurane and subsequent memory: conscious awareness with explicit memory was associated with a median CF (25th–75th centile) of 32.8 (28.4–36.7) Hz; conscious awareness without explicit memory was associated with a CF 24.8 (21.5–30.6) Hz; absence of both responsiveness and implicit memory was associated with a mean CF of 14.9 (14.2–17.3) Hz. There was a significant difference in CF associated with these different categories of memory ($P < 0.02$). We conclude that the coherent frequency of the AER reflects the likelihood of cognition during anaesthetic inhalation. (Br. J. Anaesth. 1993; **71**: 633–641)

KEY WORDS

Anaesthesia: depth. Brain: auditory evoked response, coherent frequency. Anaesthetics, volatile: isoflurane.

There is a need to produce an objective measure of depth of anaesthesia with which the anaesthetist can detect conscious awareness during light anaesthesia in patients with neuromuscular block. There is some confusion about what is meant by the term "depth of anaesthesia". The majority of papers on this subject are concerned with the relationship between a dose of anaesthetic and either somatic movement or a measurement such as EEG, heart rate, frontalis EMG or oesophageal contraction. However, all these studies give no direct information about cognitive function. In contrast, the present study has examined the changes in cognitive function produced with stepwise changes in isoflurane concentration and compared these changes with a new measurement of depth of anaesthesia derived from the auditory evoked response (AER).

There are two ways of producing the AER: the transient method and the steady state method. The middle latency part of the transient response refers to a series of one to three bipolar waves occurring in the first 100 ms after an abrupt auditory event. This middle latency response (MLR), also termed the "early cortical response", represents processing at the primary auditory cortex and is elicited using clicks presented at rates near 10 s^{-1}, although rates of as few as 1 s^{-1} produce a larger MLR but take a very long period of signal averaging to produce a satisfactory waveform. The transient MLR has been studied extensively in awake and anaesthetized patients and it looks promising as a method for measuring depth of anaesthesia [1]. However, there are two problems with the transient method: the prolonged time to produce the response (about 5 min) and difficulties in interpreting the waveforms so that conscious awareness can be inferred unequivocally from a particular waveform. In contrast to the transient method, the steady state method refers to electrophysiological activity in the EEG driven by a train of stimuli delivered at a sufficiently fast rate

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that responses evoked by successive stimuli overlap. The auditory steady state response is said to reach an amplitude maximum at rates of stimulation near 40 Hz [2]. In a personal communication, Robert Galambos suggested that the data presented in a series of papers [3–10] published from Northwick Park showed there was a dominant 40-Hz frequency before anaesthesia and this was similar to the response obtained more directly with the steady state method. All these studies [3–10] had shown that general anaesthetics caused a prolongation of the middle latency waves which are thought to contribute to the steady state response (SSR) and, consequently, it was predicted that the 40-Hz value of the dominant frequency response would decrease with anaesthesia.

Thus we decided to examine Galambos' suggestions by studying the AER when the auditory pathway was stimulated with a wide range of frequencies. At the same time, subjects inhaled a stepwise increasing, then decreasing, concentration of isoflurane. During each step, the subjects were asked also to perform tests of cognition and memory. We would thus be able to compare changes in the auditory evoked potential with psychological performance at different alveolar concentrations of anaesthetic.

SUBJECTS AND METHODS

After approval from the local medical Ethics Committee, seven anaesthetists agreed to take part in the study. The group consisted of six males and one female. None suffered from known hearing loss.

After cleaning the skin with Skinpure (Nihon Koden, Holstar Instruments, Sussex), we applied silver–silver chloride electrodes (Medicotest N-50-E, Cambac, Cambridge) to frontal and right mastoid regions with a right pre-auricular electrode as a neutral. Inter-electrode impedances were checked and maintained less than 4 kΩ. Clicks of 1 ms duration were fed to TDH 39 Headphones. The output was 65 dB greater than average hearing threshold at 6 Hz. The click generator was controlled by a CED 1401 interface and Spike 2 data acquisition software (Cambridge Electronic Design, Cambridge) running on an IBM-compatible 486 PC. The auditory stimulation sequence contained a range of 43 frequencies at 1-Hz intervals from 47 Hz to 5 Hz. The EEG amplifier had a gain of 125000 and a 1–2000 Hz bandwidth with 12 db octave^{-1} roll off. The sample rate was 1 kHz. The CED 1401 and Spike 2 program collected and averaged 100 samples of EEG at each stimulating frequency. Artefact rejection was not applied. A Fast-Fourier transform (FFT) was then applied to the evoked response at *each* frequency within the Spike 2 program. This "sweep" of frequencies was presented to the subject at all nine steps of the experiment (table I).

Derivation of coherent frequency

We found that the power in the FFT of the evoked response at each frequency usually had three components: the fundamental frequency and the first and second harmonics. Occasionally, further harmonics appeared, but were of small amplitude. Analysis of these FFT showed that, at certain frequencies, the power of the fundamental was very large, with little or no power in the harmonics (fig. 1).

Frequencies showing this pattern were termed the "coherent frequency". Frequencies on each side of it did not show this pattern, having large harmonic power. A mathematical manipulation to show up these coherent frequencies was applied so that, if:

$$[P_1+P_2] > 30\,\%\ P_f$$

where P_f is the power in the fundamental, and P_1 and P_2 are the power in the first and second harmonics, respectively, then a value of zero was applied to the P_f, otherwise P_f was left with its original value. The data were then recalculated to obtain P_r, the resultant power, using a formula which reflected the relative power in the fundamental compared with that in the harmonics and the absolute power in the fundamental. Thus:

$$P_r = \left[\frac{P_f}{P_1+P_2}\right] \times P_f$$

TABLE I. *Experimental design for the study*

				Assessment of		
Trial step	Concentration of isoflurane in oxygen (%)	Electrical stimulation to cause arousal	Coherent frequency	Within list recognition (explicit memory)	Categorization (cognitive function)	Word repetition (implicit memory)
1	Air		Yes	Yes	Yes	
2	0.2		Yes	Yes	Yes	
3	0.4		Yes	Yes		
4	0.4	Yes	Yes	Yes	Yes	
5	0.8		Yes			Yes
6	0.8	Yes	Yes			Yes
7	0.2		Yes	Yes	Yes	
8 (10 min after isoflurane)	Air		Yes	Yes	Yes	
9 (25 min after isoflurane)	Air		Yes		Category recognition for the above stimuli	Category generation and recognition for the above stimuli

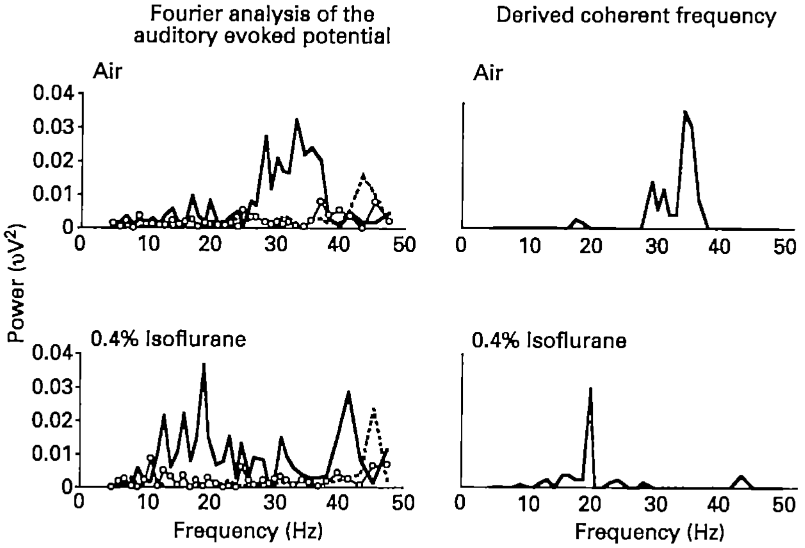

FIG. 1. Derivation of the coherent frequency for one subject. The panels on the left show the raw data plotted with the subject breathing air and then at an end-tidal isoflurane concentration of 0.4%. X axis = stimulating frequencies; Y axis = power of the resultant signal (i.e. the fourier analysis of the signal averaged EEG). The power of the fundamental is shown as a black line, whilst the 1st and 2nd harmonics are represented by open circles and a dotted line, respectively. The right hand panels show the data after the fundamental and the harmonics were transformed to obtain the coherent frequency as described in the text.

This procedure was repeated for all 43 observations and then the resultant power plotted against stimulating frequency.

Psychological tests

To validate any method of monitoring depth of anaesthesia, an independent measure of cognitive function is required. We therefore decided to examine cognitive function when volunteers breathed sub-MAC doses of isoflurane, and to test their memory function afterwards. Two tests of cognitive function were used:

(1) *A within-list recognition (WLR) test* was used to assess working memory [11]. In this test, a list of words was read out by the observer and the subject's task was to respond to repeated words. The number of intervening items between the first and second presentations of a target word varied, hence the retention interval also varied. It was assumed that performance on this task would decline as cognitive performance was compromised by increasing doses of the anaesthetic. For the WLR task, 16 lists of 23 words each served as stimuli. Each list comprised seven "target" words, each of which was repeated once, and nine "distractor" words. The target words were repeated after intervals of 0, 1, 2, 4, 8 or 16 intervening words (table II).

Two different lists were presented at each step of the experiment, apart from those steps at which the subject had an end-tidal isoflurane concentration of 0.8 % and there was no response to verbal commands (table I). The lists were read aloud by the experimenter at a rate of one word every 2 s. The subject's task was to respond to repeated words by raising the right thumb. The experimenter recorded the repetitions which were were identified correctly.

(2) *A categorization test* was used to assess general linguistic processing and attention. The subject's task was to respond to each presented exemplar of a particular category and to ignore interpolated exemplars of other categories. Relatively well-defined categories were chosen (e.g. *colours*) and familiar exemplars were used (e.g. *green*, *blue*). We also assumed that learning at the time of stimulus presentation would be reflected in subsequent memory for that stimulus, hence on recovery from the anaesthetic we tested recognition (explicit) memory for the target category exemplars.

Thus immediately after the second list of each WLR test, the subject was told that another list would be presented and that the task was to listen for the names of items belonging to a particular category, for example "metals". The experimenter then read out 20 words, of which 10 were exemplars of the specified category and 10 were distractor items from other, dissimilar, categories. The subject responded to identified exemplars by raising the right thumb. On recovery from the anaesthetic, recognition memory was tested for category exemplars presented at each of three end-tidal concentrations of isoflurane: 0%, 0.2% and 0.4%. A forced-choice procedure was used in which, for each category, pairs of exemplars were read out and the subject was asked to identify or guess which exemplar in each pair had been presented during anaesthesia.

The issue of learning under anaesthesia was examined further by reading out, 10 times, 10 exemplars of another category (e.g. *birds*, *flowers*) whilst the subject was inhaling 0.8 % isoflurane—five times before the electrical stimulation and five times afterwards. On recovery, the subjects were asked if they could recall the category to which the exemplars belonged. If they failed, four categories were named and the subject was asked to choose or guess the one from which the exemplars had been taken. The subject was then told the correct category and asked to generate as many exemplars of that category as

TABLE II. *An example of within list recognition set of words. The numerals refer to the number of other words intervening before the repetition. There are deliberately two sets of "0" words (words repeated with no gap) to test that the attention of the subject has been maintained through the list*

Word list	Number of words between repetitions
Ability	
Flavour	
Flavour	0
Dignity	
Demonstration	
Member	
Suggestion	
Character	
Suggestion	1
Segment	
Expedition	
Quantity	
Overtone	
Expedition	2
Segment	4
Bayonet	
Character	8
Liberty	
Liberty	0
Attempt	
Dignity	16
Solution	
Salvation	

possible in 1 min. The number of exemplars generated from the presented category was compared with the number generated from a matched list of *exemplars which had not been presented.* This latter test examined implicit memory [12], which is reflected in a clear influence of a prior stimulus on behaviour, even though the subject was unable to recall or recognize that item as having being presented. Recognition memory (explicit memory) for the presented exemplars was tested also, using the forced-choice procedure described above.

A note was made at each stage if the subject responded purposefully to any verbal command or stimulation. After the trial, the subject was asked also about recall of events or pain at any of the steps.

Procedure

After an overnight fast, the subject lay on a tilting bed. A 23-gauge cannula was inserted in the dorsum of the left hand. A Penlon anaesthetic machine was used to supply the isoflurane in oxygen. A Lack circuit attached to a mouthpiece was used to administer the gases to the subject, who wore a nose-clip. The subject inhaled isoflurane and the vaporizer was adjusted to reach the desired end-tidal isoflurane concentration measured by a Brüel and Kjær type 1304 anaesthetic gas monitor. When a stable end-tidal concentration was reached, the subject breathed the isoflurane for another 10 min before any measurements were performed. Monitoring also included pulse oximetry and heart rate. One anaesthetist with no other responsibilities was always assigned to monitor the subject.

EEG recordings and psychological tests were performed with the subjects breathing air and then isoflurane was administered in a stepwise fashion at concentrations listed in table I. At end-tidal isoflurane concentrations of 0.4% and 0.8% (steps 3 and 6 in table I), a peripheral nerve stimulator was used to apply a 60-mA tetanic stimulus to the left ulnar nerve for 5 s, followed by a single 200-ms duration, 1-Hz, 60-mA pulse every 1 s until the end of the stage. This was to cause and maintain arousal [13]. The psychological tests were given immediately after the tetanic stimulus and they were then followed by a recording of the EEG.

Statistics

The evoked potential data were analysed by Spike 2. The analysis of the psychological data was performed with the program *Statview 4* (Abacus Concepts Inc, CA) on an Apple Macintosh computer. Data were analysed using non-parametric tests, namely Wilcoxon rank signed test, Friedmann's test for repeated measures, Mann–Whitney *U* and Spearman's rank correlation. Significance was assessed as $P < 0.05$.

RESULTS

Coherent frequency

Figure 1 shows the transformation of the raw data to obtain the coherent frequency. The effect of isoflurane is also illustrated. If more than one peak appeared in the transformed data (which often happened with arousal), they tended to cluster and so an average CF was calculated by taking an amplitude weighted average of the coherent frequencies present for that particular sweep (fig. 1).

CF through the trial for all seven subjects are shown in figure 2. There was a variation in the initial CF, although they were all less than 41 Hz and greater than 28 Hz. Repeated measurements in the same subjects showed little variation. The CF at 0.4% and 0.8% were significantly different from those on air at the start of the trial ($P < 0.02$, Wilcoxon rank signed pair). Painful electrical stimulation of the subjects whilst breathing 0.4% end-tidal isoflurane caused an increase in the CF in three

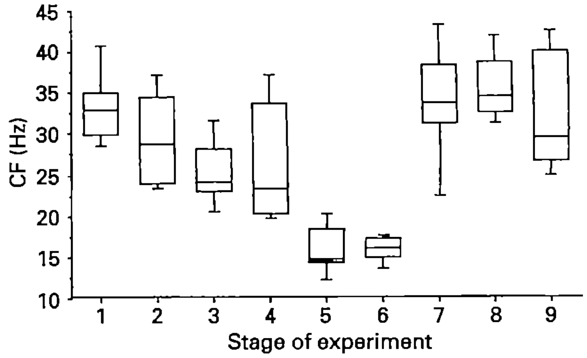

FIG. 2. Changes in coherent frequency (CF) throughout the experiment. The line within the box represents the 50th centile for the data; box edges represent the 25th and 75th centiles for the data; bars represent the 10th and 90th centiles for the data. Stages: 1 = Air; 2 = 0.2% isoflurane; 3 = 0.4% isoflurane; 4 = 0.4% isoflurane + stimulus; 5 = 0.8% isoflurane; 6 = 0.8% isoflurane + stimulus; 7 = 0.2% isoflurane; 8 = air + 10 min; 9 = air + 25 min.

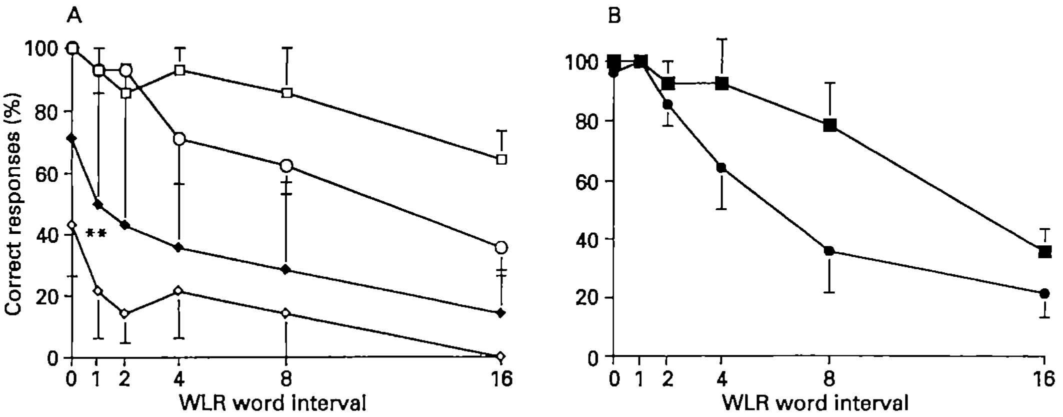

FIG. 3. Within list recognition (WLR) score (mean, SEM): A increasing end-tidal isoflurane concentration and the effect of painful stimulation; B with decreasing end-tidal isoflurane concentration. The data are shown as means with standard errors. ** Significant improvement in attending to the test between the short interval scores with 0.4% isoflurane and 0.4% isoflurane with painful stimulation ($P < 0.01$, Wilcoxon signed rank test). □ = Air; ○ = 0.2% isoflurane; ◇ = 0.4% isoflurane; ◆ = 0.4% isoflurane+painful stimulation; ■ = air (recovery); ● = 0.2% isoflurane (recovery).

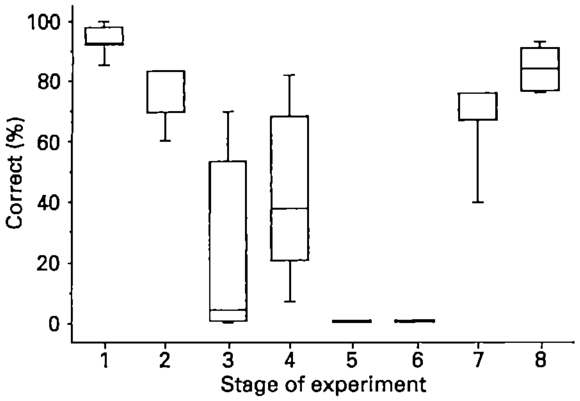

FIG. 4. Percentage correct scores for the overall within list recognition task during each step of the trial. See text for details. (These are box plots as described for figure 2.) Stages as in figure 2.

of the seven subjects, no change in two and a small decrease (2 and 6 Hz) in two subjects. This was despite obvious arousal in six of the seven subjects. Possible reasons for this result are discussed below. One subject became excited after 0.4% isoflurane (step 4) and no recordings were possible at steps 5 and 6. Subsequent recordings were possible from step 7 onwards.

Psychological tests

Within list recognition (fig. 3.) With the subject breathing air there was a decline in performance with increasing word interval. Administration of 0.2% and 0.4% end-tidal isoflurane caused a dramatic deterioration in performance, whereas painful stimulation produced an improvement in performance on the test. This reached significance only with the short word intervals (that is 0-, 1- and 2-word intervals score summed together) ($P < 0.01$ (Wilcoxon signed rank)). Even so, two of seven subjects were achieving some correct responses at the 16-word interval with stimulation in conjunction with 0.4% end-tidal isoflurane. It was noted that, although stimulation produced arousal, there was no complaint of recall of pain from any subject, although two out of seven subjects could remember receiving the tetanic stimulus (only one of these two subjects performed correctly at the 16-word interval). Performance at 0.2% end-tidal isoflurane on recovery and during air breathing appeared to be worse than at the start of the test (compare the two panels in figure 3), but this did not reach significance.

The results of the WLR for each word interval were averaged and plotted against trial step to obtain figure 4. The summed scores of long and short word intervals prevented the effect of stimulation reaching statistical significance, despite an improvement in five of seven subjects ($P = 0.12$). There was no response to the verbal word list or verbal command with 0.8% end-tidal isoflurane.

Categorization scores. These followed the same pattern as the WLR test, with a decline in performance with increasing concentration of isoflurane. Stimulation at 0.4% end-tidal isoflurane caused an improvement in performance for five individuals, but this did not reach significance for the group ($P = 0.17$, Wilcoxon rank signed test).

Category recognition (fig. 5). Memory for the categorization stimuli was assessed on recovery (when the subject had been breathing air for 25 min). Since subjects had to choose between two exemplars, only one of which had been presented previously, guessing would result in a score of 5 out of 10. There was a significant decrease in performance on this explicit memory test with the increase in concentration of end-tidal isoflurane from 0% to 0.8% ($P = 0.013$, Friedman). The performance in conjunction with 0.2% isoflurane without stimulation and 0.4% isoflurane with stimulation were not significantly different from each other. Recognition of the exemplars which had been presented in conjunction with 0.8% isoflurane was no greater than chance.

Word repetition. On recovery, the subjects were asked which category had been presented in conjunction with the greatest concentration of end-tidal isoflurane (0.8%). No subject answered correctly. Out of a choice of four possible categories, only two out of seven subjects answered correctly. The

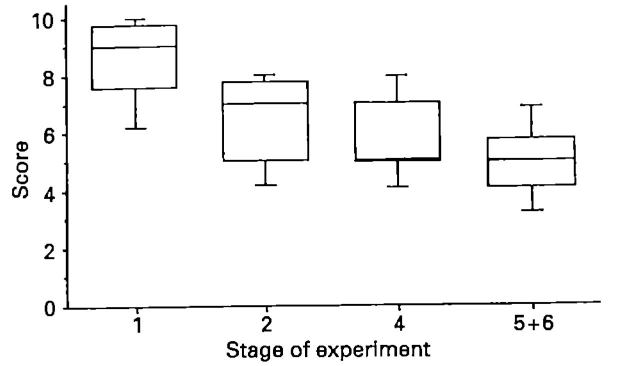

FIG. 5. Post-trial recognition scores. The subject was asked to choose between two exemplars of a category, only one of which had been presented during the trial. The maximum score was 10; chance would give a score of 5. *X* axis = concentrations of end-tidal isoflurane inhaled at the time of presentation of the *original* exemplars. This test examines explicit memory function. There is significant relationship between the dose of isoflurane and explicit memory for the exemplars ($P < 0.02$, Friedmans). The score at 0.8% end-tidal isoflurane is no greater than chance. Stages as in figure 2.

subjects were then told which category had been used and asked to name, in 1 min, as many exemplars of this category as possible. They showed no evidence of implicit memory formation for the exemplars at 0.8% end-tidal isoflurane ($P > 0.05$, Wilcoxon rank signed).

Correlation of the psychological tests with the coherent frequency

An analysis of the Spearman's correlations between the CF, WLR and CR and end-tidal isoflurane showed significant correlation between all variables ($P < 0.05$). An alternative analysis of the results is to correlate memory function with the CF obtained at that time of testing—for example, to group all the CF obtained when subjects showed no evidence of implicit memory. Three levels of psychological performance with an associated median CF (25th–75th centile) may be defined (fig. 6): 1 = *conscious awareness* (defined here as an appropriate response to a test or command during the trial) ***with explicit memory*** was associated with a median CF of 32.8 (28.4–36.7) Hz; 2 = *conscious awareness without explicit memory* was associated with CF 24.8 (21.5–30.6) Hz; 3 = *no responsiveness with no implicit memory* was present when CF was 14.85 (14.2–17.3) Hz. Levels 1 and 2 have CF which are significantly different from each other ($P < 0.02$, Mann–Whitney *U*). Similarly, levels 2 and 3 were significantly different from each other ($P < 0.0001$, Mann–Whitney *U*).

DISCUSSION

We have described derivation of the coherent frequency (CF) in the AER using a range of auditory clicks presented at frequencies in the range 5–47 Hz. There were six main findings of the study.

(1) A reduction in CF and a decline in within list recognition (WLR) and category recognition (CR) performance as the end-tidal concentration of isoflurane was increased from 0% to 0.8%. These changes reversed as the end-tidal isoflurane was decreased to 0%.

(2) Significant correlations between CF, WLR, CR and isoflurane concentration; a painful stimulus in conjunction with 0.4% end-tidal isoflurane caused an increase in CF, WLR and CR in some subjects, in addition to a significant increase in the short word interval scores in the WLR.

(3) No response of any subject receiving 0.8% end-tidal isoflurane, before or after painful stimulation.

(4) A free category generation task showed no evidence of implicit memory formation in conjunction with 0.8% isoflurane.

(5) The CF was significantly greater when conscious awareness was accompanied by explicit memory than in subjects in whom there was conscious awareness without explicit memory.

(6) The CF associated with lack of responsiveness and no implicit memory was significantly less than that associated with conscious awareness but without explicit memory.

Coherent frequency

Previous studies of the AER during anaesthesia have used 1000 samples or more of EEG at 6-Hz stimulating frequency [2]. This is because a good quality trace is essential in order to quantify the amplitude and latency of the early cortical (middle latency) waves. Recently, some groups have examined the method of updating a 1000 sample average, weighted with the most recently acquired data [14]. As we did not attempt to define a latency or amplitude, but only frequency content, 100 samples gave consistent CF values with a low variance between repeated measures and, in the pilot

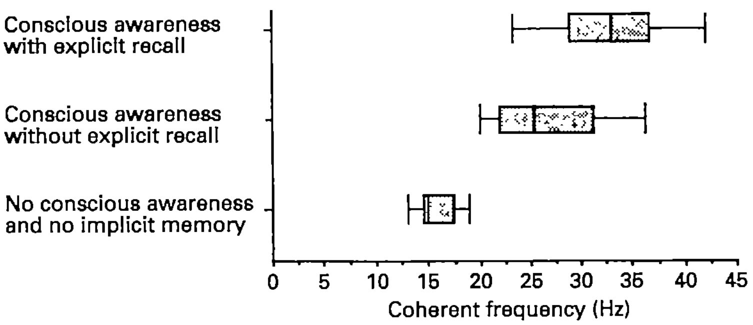

FIG. 6. The association of various coherent frequencies with subject response during the trial and with post-trial memory. See text for details.

studies breathing air, SE of CF were usually less than 1 Hz.

Fourier analysis assumes that the waveform under examination can be described as a series of sine waves of different amplitudes and phases. If the signal to be analysed is a pure sine wave, then its FFT gives rise to a single frequency with no harmonic content; however, if the signal is not sinusoid, then the harmonic content increases [15]. Galambos' description of the 40-Hz SSR seen in the awake subject was of a sine wave [16] and on this basis, by stimulating at the "correct frequency" we expected to see little harmonic content. This proved to be the case with CF in the range 28–41 Hz with the subject breathing air. The variation in frequency between subjects breathing air has been reported previously [17]; it may be related to the individual level of arousal because, in our pilot studies, the subject falling asleep during the recordings was associated with a decrease in frequency. Galambos' analysis [personal communication to J.G.J.] of the Northwick Park middle latency data [5–10] showing that the "correct frequency" would decrease with anaesthesia implied that we would expect to see smaller values of CF as anaesthesia was deepened. This was again verified in our present study.

The variation in CF between subjects seen in this study, especially in conjunction with 0.4% isoflurane, may be attributable to a number of factors; it may simply reflect the variability in frequency seen with subjects breathing air [17]; the depressant effect on CF of a dose of isoflurane may vary between subjects; there may have been difficulty in maintaining a steady state isoflurane concentration; a degree of excitation occurred in some subjects with administration of isoflurane. As the Northwick Park studies included data from both volatile and i.v. anaesthetic agents, this suggested that the CF changes reported here may be seen also with other agents. The inter-subject variation and decrease in CF with anaesthesia suggest that using a 40-Hz stimulating frequency for all subjects for monitoring depth of anaesthesia, as suggested by Plourde [18] may not be appropriate. This is discussed below.

Painful stimulation of the ulnar nerve was associated with a small but statistically insignificant increase in CF for the group in conjunction with 0.4% and no change in the CF with 0.8% end-tidal isoflurane, despite obvious changes in behaviour of the subject and performance on the psychological tests. This was probably caused by our experimental paradigm, in which the stimulation was followed immediately by the psychological tests and *then* subsequently by the measure of the CF. We felt the subjects had drifted into "deeper" anaesthesia again by the time the EEG was recorded. After completing the present study, one of the subjects was retested with the electrical stimulation during continuous EEG measurements, but without the psychological tests. This revealed that, in conjunction with 0.8% isoflurane, the initial tetanic stimulation caused a marked increase in CF, from 10 to 15 Hz, but the subsequent 1-Hz stimulation was insufficient to maintain arousal and the next recording showed a CF of 10 Hz. This problem of selecting a sustained stimulus to represent surgical arousal will be more easily addressed in a study undertaken during a surgical operation.

Psychological tests

There was a decline in cognitive function with increasing dose of isoflurane, as shown by the WLR and CR results. Six of the seven subjects continued to respond when receiving 0.2%, and four with 0.4% isoflurane. The CF recorded at times when there was no explicit recall of events afterwards were significantly different from those recorded in other periods when the subjects showed no explicit memory for events. Painful stimulation caused an increase in overall performance in individuals with both tests, but this was not significant for the group as a whole. A more detailed analysis of the WLR test revealed an increase in performance at the short word interval scores. This would imply an effect on attention and short-term or working memory, but not on long-term memory. The scores for longer word intervals represent performance with increasing task difficulty and scores did not increase significantly for the group as a whole with stimulation in conjunction with 0.4% isoflurane, although two individuals began to respond correctly with painful stimulation. These results confirm that the overall state of arousal (and cognitive processing) of a subject is determined by the balance between the depressant effects of anaesthetics and the stimulation the subject receives. The implications for anaesthetic practice are obvious: that a previously unresponsive patient may become responsive with surgical stimulation, and care must be taken to avoid arousal to state of conscious awareness, especially if the patient is paralysed.

Post trial recall

The post-experiment category recognition tests revealed that there was a significant decline in explicit recall with increasing dose of isoflurane. These results confirm previous work [19–22] (fig. 6). There was no evidence of implicit memory formation in conjunction with 0.8% isoflurane. There are a number of possible explanations for this latter result: the words used were not salient enough [23]—although other authors have found evidence of implicit memory using this type of stimulus [24]; the number of word repeats consisted of only 10 repetitions, but there is some evidence that more presentations may allow learning to take place [25]; and there was not enough arousal even with ulnar nerve stimulation, implying that when implicit memory formation is found with greater concentrations of isoflurane, it may be because the surgical stimulation was enough to reverse the depressant effects of the anaesthetic. Finally, the WLR and CR tests preceding and following the 10 critical repetitions may have interfered with the implicit memory trace or its retrieval.

Comparison of the 10-Hz transient MLR and the 40-Hz SSR with the CF

Previous studies using the 40-Hz SSR showed that the amplitude of the EEG response is markedly reduced with anaesthesia at a time when there is loss of responsiveness of the patient to a button-pressing task. The reappearance of the 40-Hz SSR coincided with the patient beginning to respond to the button-pressing task [26, 27]. However, a recent study showed that implicit memory formation can still be demonstrated when the 40-Hz SSR is attenuated [28]. The result may be explained by the original suggestion of Galambos [R. Galambos, personal communication to J. G. J.] that, with lengthening of the MLR with anaesthesia, the 40-Hz stimulating frequency may no longer be appropriate. Thus a large reduction in the amplitude of the 40-Hz SSR with anaesthesia may not simply reflect reduction in attention or vigilance, but also a reduction in the coherent frequency of the brain. Another study comparing the 40-Hz SSR and the MLR showed that, whilst the latter was affected in a dose-dependent manner by the anaesthetic, the 40-Hz SSR was dramatically and maximally reduced during enflurane anaesthesia, irrespective of the concentration given [29].

In summary, the 40-Hz SSR is probably too sensitive a variable to measure information processing. Madler and colleagues [30], using a frequency analysis of the middle latency waves, showed a decrease in the dominant frequency from 40 Hz to about 10 Hz with concentrations of isoflurane increasing from 0% to 1.2%. Thus the variable frequency stimulating paradigm which generates the coherent frequency used in our study may be more appropriate.

Relationship between the coherent frequency, psychological performance and post-trial memory

The correlation of specific frequencies with psychological performance should be treated with some caution—as we have no evidence (or, indeed, test) of implicit memory in other conditions, we cannot exclude the possibility that our test is simply insensitive. Furthermore only seven subjects have been studied using this paradigm and it would be necessary to study a greater number of subjects to determine the clinical relevance of the findings. However, the coherent frequency/psychological performance correlation confirms recent studies which examined the presence or absence of the middle latency waves along with tests of implicit and explicit memory during anaesthesia [31]. With both the isoflurane and propofol techniques, no post-anaesthetic explicit or implicit memory could be demonstrated. Furthermore, the AER showed that the middle latency waves were abolished and a Fourier analysis revealed a frequency of about 10–15 Hz. However, with the benzodiazepine–fentanyl technique, an implicit memory task showed evidence of learning in this group, along with preservation of the middle latency and a Fourier analysis showing a frequency of about 40 Hz. In another study, signs of movement during operation were correlated with the re-appearance of the MLR and a dominant power spectrum frequency of approximately 40 Hz. Conversely, a supressed MLR, with a low spectrum frequency of 10–20 Hz, was not associated with movement [32]. These frequencies in both studies are similar to those seen in figure 6.

In summary, the coherent frequency was derived from the AER after Fourier transform. The coherent frequency, along with psychological tests, showed consistent changes with anaesthetic administration and stimulation. We suggest also that a relationship between responsiveness during the trial, post-trial memory and a particular range of coherent frequency may exist.

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EFFECT OF A SUB-ANAESTHETIC CONCENTRATION OF HALOTHANE ON THE VENTILATORY RESPONSE TO SUSTAINED HYPOXIA IN HEALTHY HUMANS

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SUMMARY

We selected nine normal subjects (8M, 1F; aged 25–43 yr) with brisk hypoxic ventilatory responses, and studied their ventilatory response to sustained isocapnic hypoxia (Sa_{O_2} 82 (SEM 0.1) % for 25 min) in the presence and absence of 0.1% inspired halothane. Halothane had no significant effect on baseline ventilation or gas exchange. In the absence of halothane, ventilation increased initially from mean 7.57 (0.35) litre min^{-1} to 14.54 (0.91) litre min^{-1}, and decreased subsequently to 10.74 (0.32) litre min^{-1} during hypoxia (both $P < 0.05$). In the presence of 0.1% inspired halothane, ventilation increased initially from 7.19 (0.47) litre min^{-1} to 12.08 (0.99) litre min^{-1} ($P < 0.05$), then decreased to 10.12 (0.28) litre min^{-1} during sustained hypoxia (ns compared with baseline normoxic ventilation). Halothane reduced significantly the initial increase in ventilation ($P < 0.05$), but did not enhance the subsequent decrease. These results confirm that a sub-anaesthetic concentration of halothane depresses the initial hypoxic ventilatory response; the response during prolonged periods of hypoxia is, however, less than the initial response and is reduced in the presence or absence of a sub-anaesthetic concentration of halothane. (Br. J. Anaesth. 1993; **71**: 642–647)

KEY WORDS

Anaesthetics, volatile: halothane. Hypoxia: ventilatory responses.

Halothane, given in anaesthetic concentrations of 1 MAC to humans, depresses resting ventilation under normoxic conditions and abolishes the hypoxic ventilatory response [1, 2]. These effects, although clinically important, are present when the patient is supervised during anaesthesia. Knill and Gelb [1], however, have shown that even a sub-anaesthetic concentration of halothane (0.1 MAC), which does not alter resting ventilation, suppresses the ventilatory response to hypoxia, possibly by a direct action on the carotid body chemoreceptors [3–6]. This effect has important clinical consequences, as sub-anaesthetic concentrations are present after operation when patients are relatively unsupervised. Suppression of the hypoxic ventilatory response would therefore be hazardous in patients after operation, as large clinical studies have reported frequent hypoxaemia in recovery room patients [7, 8].

Evidence that sub-anaesthetic concentrations of halothane suppress the ventilatory response to hypoxia in humans comes exclusively from one group of investigators [1, 2, 6]. Studies in animals [9–11] have not displayed this effect, showing only about a 50% reduction in the hypoxic ventilatory response with anaesthetic concentrations of halothane. Although these discrepancies may arise from species differences, the effect of sub-anaesthetic doses in humans warranted verification because of the clinical implications for postoperative patient care.

The effect of sub-anaesthetic concentrations of halothane on the ventilatory response to sustained hypoxia is also of interest. It is now well documented [12–14] that the ventilatory response to a sustained isocapnic hypoxic stimulus which lasts longer than about 10 min is biphasic, with an initial increase followed by a subsequent decrease towards the normoxic baseline value. The secondary reduction in ventilation is not caused by changes in cerebral blood flow, and hence brain $P\text{CO}_2$, resulting from the hypoxia [15]. The exact mechanism is uncertain, but may be a reduction in peripheral chemosensitivity [14]. Because halothane may act at this site [6], hypoxaemic episodes which develop after anaesthesia may be more severe when halothane is present and the response to hypoxia is attenuated.

We have studied, therefore, the effect of approximately 0.1 MAC halothane on the ventilatory response to sustained hypoxia in normal subjects to see if a sub-anaesthetic concentration of halothane suppresses the initial increase and enhances the subsequent decrease in ventilation.

SUBJECTS AND METHODS

We studied 18 subjects: nine (eight male, one female; aged 25–43 yr) had an initial increase in ventilation of 20% or more on the first visit (see Study plan) and

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were studied further. All had normal values for ventilatory capacity (FEV$_1$ 93–122% predicted; FVC 85–127% predicted) and none had a history of cardiorespiratory disease. None was taking any medication at the time of study or had received halothane for anaesthesia previously. Local Ethics Committee permission was obtained and all subjects gave written informed consent.

The subjects breathed through a low-resistance valve with a deadspace of 90 ml. The inspiratory port was connected to a five-way valve (Hans Rudolf 5-way Gatlin Valve Series 2430) which allowed the inspired gas mixtures to be changed abruptly without the subject's knowledge. Expiratory gas passed via a heated pneumotachograph (Fleisch No. 2) through mixing and drying chambers to a Parkinson Cowan CD4 dry gas meter modified to give a digital output. The integrated expiratory flow signal, which gave breath-by-breath tidal volume, was calibrated against the output of the CD4 gas meter every 10 litre to correct for drift of the flow signal. Inspiratory and end-tidal oxygen (PI_{O_2}, PE'_{O_2}) and carbon dioxide PI_{CO_2}, PE'_{CO_2}) partial pressures were measured at the lips with a mass spectrometer (VG Spectralab-M) calibrated previously with five gas mixtures of known concentrations of oxygen, carbon dioxide, nitrogen and argon. Ear arterial oxygen saturation (Sa_{O_2}) was recorded continuously using a Hewlett–Packard 47201A ear oximeter adapted to give a fast response time of 1.6 s [16]. The electrocardiogram was also monitored throughout. Analog signals were digitized using a DEC PDP 11/23 computer and custom written programs provided breath-by-breath values for ventilatory frequency (f), tidal volume (VT, BTPS), instantaneous ventilation ($\dot{V}E^{inst} = f \times V$T, BTPS), mean inspiratory flow (VT:TI), inspiratory time:total breath time ratio (TI:TT), Sa_{O_2}, PE'_{O_2}, and PE'_{CO_2}. Data were recorded on disk and analysed off-line using a DEC PDP 11/73 computer.

Oxygen consumption ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$), both expressed as litre min^{-1} STPD, were measured over a 2-min period using a digital output from the dry gas meter and the oxygen and carbon dioxide concentrations of mixed expired gas sampled simultaneously from the mixing chamber. Oxygen concentration was measured using a Servomex O_2 analyser (model 570A) calibrated previously with air and 100% nitrogen, and carbon dioxide was measured with a Gould capnograph (mark III) calibrated with four gas mixtures of known carbon dioxide concentration.

Ventilatory response to sustained hypoxia

Measurements were made with the subject seated at rest. Initially, they breathed room air for 15 min with duplicate measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ made between 10 and 14 min. Sa_{O_2} was then reduced to 80–85% for 25 min. A rapid onset of hypoxia was achieved by giving the subject three breaths of 100% nitrogen followed by an inspired oxygen concentration of approximately 10%. Similarly, at the end of hypoxia, a rapid return to normoxia was produced by taking two breaths of 100% oxygen before returning to room air. All changes in inspired gas concentrations were made during expiration. Carbon dioxide was added manually to the inspired gas to keep PE'_{CO_2} as close as possible to the baseline normoxic value.

Administration of halothane

Halothane was administered using a Cyprane Fluotec Mark 3 vaporizer. The inspired concentration was adjusted as necessary to maintain an inspired concentration of 0.1% throughout. Concentrations were measured at the lips with a Bruel and Kjaer halothane analyser (model 1304). Mean values were recorded for each 1 min using a custom-written program on a BBC microcomputer.

Study plan

The subjects attended the laboratory on two occasions. The first visit constituted a familiarization and screening study. A medical history was taken and FEV$_1$ and FVC were measured to confirm normal lung function. The ventilatory response to sustained hypoxia was then measured. Subjects were recruited for the definitive study only if the initial increase in ventilation in response to hypoxia was 20% or more.

On the second visit, the ventilatory response was measured in duplicate. On one occasion, halothane was added to the inspired gas for the entire measurement period, and on the other no halothane was used. The order of the studies was randomized, and the two measurements separated by at least 60 min of breathing room air to ensure that the halothane was fully excreted and there was full recovery of the hypoxic ventilatory response [13].

Analysis and statistics

Group data are given as mean (SEM). In each subject, mean values were calculated for baseline normoxia (A1: 4 min immediately before onset of hypoxia); early hypoxia (H1: minutes 3–6 of hypoxia); late hypoxia (H2: minutes 14–17 of hypoxia); and normoxic recovery phase (A2: minutes 2–5 after the return to breathing room air).

Measurements were made between 14 and 17 min of hypoxia because, in two subjects, the breathing pattern after 18 min of hypoxia became too irregular for accurate analysis. For technical reasons, data also were not available for the end of hypoxia and recovery periods in a further one subject. Longitudinal comparisons were therefore made using data from eight subjects, using Analysis of Variance with the Sheffé test for comparison of all possible pairs. Comparisons between control and halothane were made using Student's paired t test.

RESULTS

The mean (SEM) inspired halothane concentration measured throughout the nine studies was 0.10 (0.01)%; mean end-tidal halothane concentration was 0.05 (0.003)%. Before hypoxia was induced, halothane had no significant effect on gas exchange, ventilatory pattern, oxygen saturation or PE'_{CO_2} (table I).

In both the control and the halothane studies, a reduction in Sa_{O_2} to approximately 80% (fig. 1)

TABLE I. *Baseline normoxic values (mean (SEM)) for gas exchange, ventilatory variables, oxygen saturation and end-tidal* P_{CO_2}. *No significant differences between groups*

	Control	Halothane
$\dot{V}_{O_2}$ (litre min^{-1})	0.24 (0.01)	0.26 (0.01)
$\dot{V}_{CO_2}$ (litre min^{-1})	0.22 (0.01)	0.22 (0.01)
Gas exchange ratio	0.91 (0.03)	0.95 (0.04)
$\dot{V}_E^{inst}$ (litre min^{-1})	7.57 (0.35)	7.19 (0.46)
V_T (litre)	0.59 (0.04)	0.57 (0.04)
f (b.p.m.)	13.5 (0.9)	13.3 (1.0)
$V_T:T_I$ (litre s^{-1})	20.9 (1.16)	20.1 (1.8)
Sa_{O_2} (%)	96 (0.5)	96 (0.5)
$P_{E'CO_2}$ (kPa)	5.21 (0.12)	5.31 (0.08)

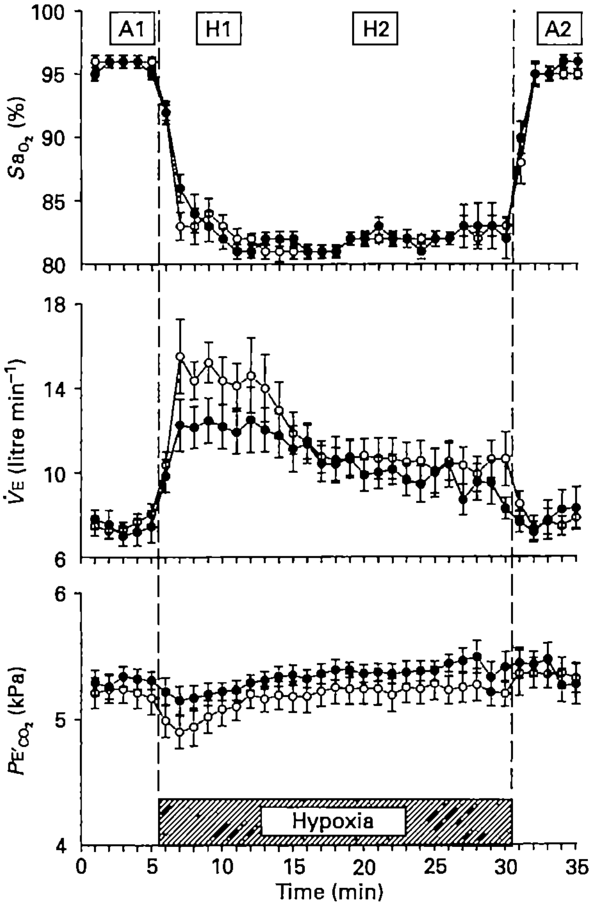

FIG. 1. Ear oxygen saturation (Sa_{O_2}), instantaneous minute ventilation ($\dot{V}_E^{inst}$ ($\dot{V}_E$ on graph)) and $P_{E'CO_2}$ plotted against time during the control (○) and halothane (●) studies (mean, SEM for each 1-min period for all subjects). For each subject, mean values for each variable were calculated over the periods A1 (baseline normoxia), H1 (early hypoxia), H2 (late hypoxia) and A2 (recovery normoxia).

caused an initial increase, followed by a subsequent decrease, in $\dot{V}_E^{inst}$ (fig. 1). $P_{E'CO_2}$ was maintained within 0.3 kPa on average (fig. 1).

There were no significant differences in $\dot{V}_E^{inst}$, V_T, f or $V_T:T_I$ ratio recorded during the normoxic periods before and after hypoxia in either the control or halothane studies (table II). In both control and halothane studies, hypoxia caused an initial increase in $\dot{V}_E^{inst}$ which was significantly different from both the baseline and recovery normoxic periods ($P < 0.05$) (table II). In the control study, $\dot{V}_E^{inst}$ was significantly greater ($P < 0.05$) during early than during late hypoxia (table II). However, the decline was not significantly different in the halothane study, although the consecutive mean values showed a similar trend (fig. 1).

The changes in $\dot{V}_E^{inst}$ in both the control and halothane studies were largely caused by changes in V_T, with no significant changes in f (table II). In both studies, there was a significant increase ($P < 0.05$) in $V_T:T_I$ during early hypoxia. In the control study, $V_T:T_I$ during early hypoxia was also significantly greater ($P < 0.05$) than that during the recovery normoxic period (table II). In the halothane study, $\dot{V}_E^{inst}$ was significantly less ($P < 0.05$) than control during early hypoxia, but not during late hypoxia (fig. 2); similar results were obtained for $V_T:T_I$. There were no significant differences in V_T or f between the two studies at any time.

Sa_{O_2} and $P_{E'O_2}$ were similar in the two studies at each of the four times of measurement (table II). $P_{E'CO_2}$ did not change significantly during either the control or halothane studies (table II), but $P_{E'CO_2}$ was slightly but significantly ($P < 0.05$) smaller in the control than the halothane study during early hypoxia. There was no significant difference in heart rate between the control and halothane studies at any of the four times (table II).

DISCUSSION

In normal subjects, we have shown that a sedative concentration of halothane reduced significantly the stimulation of ventilation which occurs within the first 10 min of exposure to hypoxia. These results confirm the findings of Knill and Gelb [1], who showed that sedation with halothane reduced significantly the hypoxic ventilatory response in humans using the progressive isocapnic method. This method imposes a gradual reduction in $F_{I_{O_2}}$ over a period of 8–10 min. The smaller effect of halothane seen in the present study (an approximately 30% reduction in response compared with 70% reported by Knill and Gelb [1]) may have been caused partly by the inadvertent hypocapnia at the start of hypoxia in the control study, which would reduce the response and thus lead to an underestimation of the ventilatory response to hypoxia without halothane during this initial period. However, the absolute level of ventilation after exposure to hypoxia for more than 15 min was not affected significantly by halothane.

We did not wish to expose more subjects to the combination of hypoxia and halothane than was necessary, because of the known, albeit unlikely, risk of liver damage. Subjects who responded to hypoxia were therefore selected deliberately so that the total number studied could be minimized. We cannot exclude the possibility that individuals with a low initial ventilatory response to hypoxia may respond to a combination of hypoxia and halothane in a different manner, thus limiting the relevance of these findings to the general population. The fact that the mean initial increase in ventilation in our study is greater than that reported by Easton, Slykerman and Anthonisen [12] would suggest also that we have studied an atypical population. However, only four

TABLE II. *Ventilatory variables, ear oxygen saturation and end-tidal gas tensions (mean (SEM)) during the control and halothane studies.* * *Significant difference* ($P < 0.05$) *compared with early hypoxia value*

	Normoxia Baseline	Hypoxia Early	Hypoxia Late	Normoxia Recovery
$\dot{V}_E^{inst}$ (litre min^{-1})				
Control	7.57 (0.35)*	14.54 (0.90)	10.74 (0.32)*	7.58 (0.18)*
Halothane	7.19 (0.47)*	12.08 (0.99)	10.12 (0.28)	7.86 (0.28)*
V_T (litre)				
Control	0.59 (0.04)*	0.99 (0.07)	0.75 (0.06)*	0.60 (0.05)*
Halothane	0.57 (0.04)*	0.89 (0.10)	0.72 (0.08)	0.62 (0.06)
f (b.p.m.)				
Control	13.4 (0.9)	15.1 (0.7)	14.4 (0.7)	13.3 (1.2)
Halothane	13.3 (1.0)	14.3 (1.0)	14.6 (0.9)	13.1 (1.0)
$V_T:T_I$ (litre s^{-1})				
Control	20.9 (1.2)*	36.5 (2.1)	28.2 (2.6)	21.8 (1.9)*
Halothane	20.1 (1.8)*	31.6 (2.7)	28.2 (2.7)	23.5 (2.9)
Sa_{O_2} (%)				
Control	96 (0.5)*	83 (2.9)	82 (1.1)	95 (1.5)*
Halothane	96 (0.5)*	83 (3.0)	82 (1.4)	96 (1.4)*
$P_{E'_{CO_2}}$ (kPa)				
Control	5.21 (0.12)	5.03 (0.38)	5.23 (0.37)	5.35 (0.32)
Halothane	5.31 (0.08)	5.22 (0.24)	5.37 (0.20)	5.36 (0.36)
$P_{E'_{O_2}}$ (kPa)				
Control	13.81 (0.20)*	6.80 (0.17)	6.81 (0.19)	12.85 (0.61)*
Halothane	13.79 (0.26)*	6.83 (0.16)	6.84 (0.19)	13.47 (0.46)*
HR (beat min^{-1})				
Control	63 (4)	76 (4)	69 (4)	60 (4)
Halothane	62 (3)	74 (4)	69 (4)	60 (3)

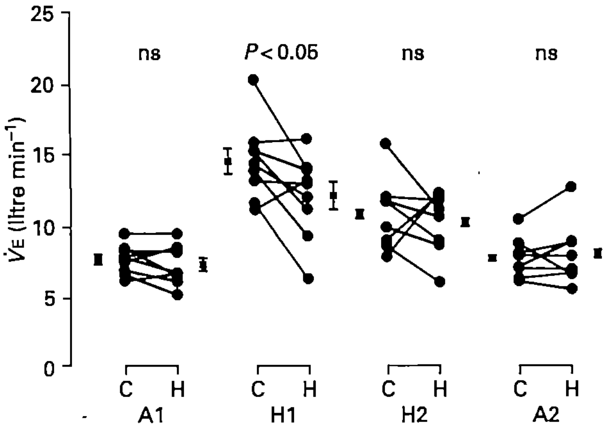

FIG. 2. Comparison of total ventilation during the control (C) and halothane (H) studies in each subject (●) for periods A1 (baseline normoxia), H1 (early hypoxia), H2 (late hypoxia) and A2 (recovery normoxia). Mean values (■) and SEM are also given for the group data.

of an initial 18 subjects recruited for the study were rejected because their initial ventilatory response to hypoxia was less than 20%. The remaining five subjects were not studied for several other reasons. Furthermore, our subjects were predominantly male, whereas approximately 50% of those studied by Easton's group [12] were female. This gender difference may account for the relatively large initial increase in ventilation in our subjects in the control study, as men are known to have a greater hypoxic ventilatory response than women [17]. Our results are similar to those reported in the male population by Suzuki and colleagues [15]. The subjects we studied would therefore seem to be fairly representative of the normal population, at least for men.

We chose to administer 0.1% halothane and monitor the end-tidal concentration rather than attempt to adjust the inspired concentration in order to maintain a constant end-tidal concentration. This was primarily because the resolution of the digital output from the analyser was limited at this concentration, and secondarily because fluctuations in end-tidal halothane concentrations over short periods would not necessarily reflect cerebral concentrations. In addition, previous evidence suggested that after about 15 min of 0.1% inspired halothane, the end-tidal concentration was likely to be in the desired range of 0.05–0.07% [18].

The extent to which halothane affects the initial ventilatory response to hypoxia appears to vary between species. Anaesthetic concentrations of halothane have been shown to cause a 50–70% reduction in the ventilatory or chemoreceptor response to hypoxia in cats [4], dogs [9] and goats [11], whereas our study, and that of Knill and Gelb [1] demonstrated 30% and 70% reductions, respectively, with sedative concentrations only. As species differences in carotid body histochemistry [19, 20] and pathophysiological responses to hypoxia [21, 22] are well documented, this finding is not surprising, and merely reinforces the fact that results obtained in animal models may not always predict the response in humans.

The mechanism of the secondary decline in ventilation during hypoxia remains unclear. It was suggested initially [12] that sustained hypoxia released a central neuro-inhibitory substance such as adenosine or gamma aminobutyric acid. However, Khamnei and Robbins [14] argued that, if central respiratory neurone activity was depressed in this way, ventilation should decrease to less than before hypoxia on removal of the hypoxic stimulus. As they and others [12] were unable to demonstrate such an effect in adult humans, it was suggested that the secondary reduction in ventilation was the result of peripheral chemoreceptor attenuation. This study confirms the absence of an undershoot in ventilation on removal of the hypoxic stimulus in the presence or absence of halothane—an observation which merely suggests that hypoxia does not have a persistent direct depressant effect on central respiratory neurones. Although absence of an undershoot is compatible with the hypothesis that the secondary decline in ventilation is the result of peripheral chemoreceptor attenuation, it does not exclude the possibility that responses to chemoreceptor input are being modified centrally. Furthermore, direct measurements of carotid sinus nerve activity in animals do not support consistently the proposal of peripheral chemoreceptor attenuation. Whilst a decrease in carotid sinus nerve activity during sustained hypoxia has been demonstrated in rabbits [23, 24], this has not been observed in cats [25, 26] and goats [27]. Although this may again indicate a species difference, the hypoxia (Pa_{O_2} 2.2–4.7 kPa) studied in the rabbits was more severe than that studied in cats, goats and humans [12, 14], in which Pa_{O_2} values of 5.3–6.6 kPa have been used. The decrease in chemoreceptor activity during sustained hypoxia seen in rabbits may therefore be a consequence of the degree of hypoxia studied, particularly as Kaiying, Ponte and Sadler [24] found that the adaptation in carotid sinus nerve discharge became more pronounced as the severity of hypoxia was increased.

Indirect estimates in humans [6] and direct neural recordings in cats [3, 4] suggest that halothane acts at the peripheral chemoreceptors. However, halothane has also been shown to act centrally, at least in cats [10, 28]. In this study, we cannot exclude the possibility that halothane was acting centrally, as the concentration used is known to produce other central effects such as sedation [29, 30]. The observation that halothane reduced the initial ventilatory response, but did not alter ventilation during sustained hypoxia, is consistent with the possibility that the peripheral chemoreceptor response is facilitated initially by a central mechanism [31] which wanes subsequently if exposure to hypoxia is continued. Such cortical facilitation may be susceptible to sedative drugs. This proposal is compatible with the findings of Chin and colleagues [32], who found an increased rate of onset of the secondary decline in ventilation during stage 2 sleep in humans which they attributed to the removal of a behavioural component of the biphasic hypoxic ventilatory response. The mathematical model of the ventilatory response to sustained hypoxia described by Khamnei and Robbins [14] is compatible with mechanisms other than peripheral attenuation and more work is needed to determine the exact processes involved in the biphasic hypoxic ventilatory response in humans.

After general anaesthesia, hypoxaemia is frequent and may be severe. Episodes of hypoxaemia are more common in smokers and the elderly and may occur despite routine oxygen therapy [7]. Usually, such episodes of hypoxaemia are short (median duration 1 min), but they occasionally last much longer. These episodes are probably caused by transient airway obstruction. Recovery appears to depend on arousal, presumably in part resulting from peripheral chemoreceptor stimulation [33]. The influences of residual anaesthetics, such as the modern volatile agents, are likely to persist for up to 2 h [18] and could thus contribute to many hypoxaemic episodes [7]. The present study suggests that, although residual volatile anaesthetic agents may increase the danger of transient episodes of hypoxaemia, the response to longer periods of hypoxia is reduced regardless of the presence or absence of residual anaesthetic agent.

ACKNOWLEDGEMENT

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COMPARISON OF THE EFFECTS OF THE LARYNGEAL MASK AIRWAY AND ENDOTRACHEAL INTUBATION ON VOCAL FUNCTION

S. K. LEE, K. H. HONG, H. CHOE AND H. S. SONG

SUMMARY

*We have compared changes in vocal function produced after insertion of a laryngeal mask airway (LMA) with those produced by tracheal intubation in 20 patients. Using acoustic waveform analysis, we computed amplitude variability (AV), pitch variability (PV), harmonics-to-noise ratio (HNR) and additive noise level (ANL) before anaesthesia and at 1, 4, and 24 h after tracheal extubation. There were no significant changes in vocal function after extubation except for HNR ratio (*P = 0.046*) at 4 h in the LMA group. There were differences in all four variables at 1 h, 4 h, or both, after tracheal extubation compared with baseline in the tracheal tube group. In both groups, all variables were the same as baseline values 24 h after extubation. We observed significant differences in AV (4 h), PV and ANL (1, 4 h) values between the two groups. These observations suggest that the LMA causes less vocal change than tracheal intubation (*Br. J. Anaesth. 1993; **71**: 648–650)

KEY WORDS

Intubation: laryngeal mask airway, tracheal tube. Complications: laryngeal function.

It is well known that tracheal intubation produces voice changes [1, 2]. The laryngeal mask airway (LMA) is used as an alternative to tracheal intubation [3–6], but its effect on vocal changes has not been studied. We have therefore measured voice changes in the first 24 h after a standard anaesthetic in patients allocated randomly to the use of either an LMA or a tracheal tube.

PATIENTS AND METHODS

After obtaining written informed consent and approval from the Hospital Ethics Committee, we studied 20 males (ASA grade I) undergoing minor elective orthopaedic procedures of the upper or lower extremity. Patients were excluded if they had respiratory tract disease, anatomical abnormalities of the upper airway or hearing problems, or if they were smokers. They were also excluded from the study if either a tracheal tube or an LMA could not be placed into the airway at the first attempt. The patients were allocated randomly to one of two groups according to the use of either LMA or tracheal tube: LMA group ($n = 10$): LMA without laryngoscopy; tube group ($n = 10$): tracheal intubation using tracheal tube with laryngoscopy (blade No. 3, curved type) through the orotracheal route. The mean (range) age and body weight of the patients were 26.5 (19–38) yr and 64.6 (57–77) kg in the LMA group and 22.7 (22–27) yr and 65.8 (58–76) kg in the tube group, respectively. The patients were blinded to the study group.

No premedication was given and all operations were carried out under general anaesthesia, induced with thiopentone 5 mg kg^{-1} and either orotracheal intubation or LMA insertion facilitated using suxamethonium 1.5 mg kg^{-1}. A No. 3 LMA (Intravent, Pacific Medical Supplies Pty Ltd, Australia) was used in the LMA group and a low-pressure, high-volume cuffed tracheal tube of 7.0-mm P.V.C. (Sheridan, U.S.A.) in the tube group. Anaesthesia was maintained with 50 % nitrous oxide and 1–1.5 % halothane in oxygen. Neuromuscular block was produced with pancuronium 0.1 mg kg^{-1} and subsequent incremental doses were given as necessary. Monitoring was performed in our routine manner. The patient was placed supine with the head in a neutral position using a ring support. At the end of surgery, residual neuromuscular block was antagonized with neostigmine 35 µg kg^{-1} and atropine 20 µg kg^{-1}. The mean durations of intubation were 97.5 min (range 45–170 min) in the LMA group and 105.5 min (range 50–180 min) in the tube group.

Acoustic analysis

The voice was recorded on an ordinary magnetic tape with a digital tape-recorder in a noiseless room, on the morning of surgery (preanaesthesia) and after full recovery from general anaesthesia (clear mental state and adequate skeletal muscle power), at 1, 4 and 24 h after extubation. A mouth-to-microphone distance of about 10 cm was maintained during tape recording. Each patient was instructed to phonate the Korean vowel /e/ at least three times.

Voice samples for the vowels were low-pass

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filtered and digitized through a 12-bit A/D converter at a sampling rate of 30 kHz. Segments of the voice samples (0.5 s) were extracted by excluding the initial and final portions from each sample and were stored on floppy disc for subsequent analysis, conducted by IBM-compatible personal computer and a software program for voice analysis devised by one of the authors (K.H.H.). The voice analyst was blinded to the study group.

We calculated the extent of pertubation for roughness. Pitch variability (PV) is a measure of how the pitch of the voice (in a single vowel sound) varies over short time periods. Therefore, PV is the coefficient of variation (CV) (CV = SD/Mean × 100 %) of the time intervals between adjacent peaks of waveforms. Amplitude variability (AV) is the amplitude change between adjacent peaks of waveforms and expressed as CV (%).

For noise level determination, harmonics-to-noise ratio (HNR) and additive noise level (ANL) were obtained. HNR was calculated from the acoustic waveform by a peak picking method [7]. Harmonics is the energy of the average waveform, while noise is the mean energy of the difference between the individual and the average waveform. Thus HNR is a particular form of signal-to-noise ratio. ANL is the energy of noise from the actual waveforms within the frequency range greater than 1 KHz; it was obtained directly from adaptive comb-filtered acoustic waveforms using Fast-Fourier transform with a Hamming window.

Statistical analysis

Results are expressed as mean (SD). The Wilcoxon signed-rank test was used for statistical analysis of the PV and AV values within each group at different times of measurement. HNR and ANL values for intragroup comparisons were compared using Student's paired t test for parametric data. Between group comparisons were made using Student's unpaired t test. $P < 0.05$ was considered significant.

TABLE I. *Differences of each variable from baseline value at 1, 4 and 24 h (mean (SD)). AV = Amplitude variability; PV = pitch variability; HNR = harmonics-to-noise ratio; ANL = additive noise level. ns = Not significant*

	Change from the baseline values		P for difference between groups
	LMA group	Tube group	
AV (%)			
1 h	0.22 (0.57)	0.70 (0.77)	ns
4 h	0.28 (0.67)	1.04 (0.79)	0.031
24 h	0.18 (0.55)	−0.13 (0.74)	ns
PV (%)			
1 h	0.18 (0.47)	0.82 (0.56)	0.012
4 h	0.31 (0.66)	1.11 (0.78)	0.023
24 h	−0.09 (5.57)	−0.11 (0.36)	ns
HNR (dB)			
1 h	−3.08 (5.63)	−3.07 (7.98)	ns
4 h	−3.78 (5.23)	−7.58 (6.48)	ns
24 h	−0.55 (3.47)	3.65 (7.48)	ns
ANL (dB)			
1 h	1.10 (4.00)	5.75 (5.07)	0.033
4 h	1.25 (3.91)	6.68 (3.76)	0.005
24 h	0.73 (4.25)	−3.28 (5.34)	ns

RESULTS

All four measures of vocal change were worse than baseline at 1 and 4 h in both groups, but the values had largely returned to baseline by 24 h. Several of these changes were significant for the tube group, but only one for the LMA group. Five of the eight differences between groups (at 1 and 4 h) were statistically significant (table I).

DISCUSSION

The LMA was first used in anaesthesia as an alternative to tracheal intubation by Brain in 1983 [8] and has been used safely in general anaesthesia for children and adults in spontaneously breathing patients and those undergoing controlled ventilation [9–12]. There should be little possibility of an LMA damaging the vocal cord or the other intralaryngeal structures which may change vocal function, but in contrast, laryngeal complications, including hoarseness, may develop after short-term or long-term tracheal intubation [13–16]. It has been reported that LMA placement was associated with a smaller incidence of sore throat than tracheal intubation [17].

A computer system is widely applicable for voice analysis in clinical practice [18] and many acoustic parameters have been developed [7, 19–23]. New terms have been devised: "jitter" is the cycle-to-cycle variation in pitch which we have measured as "pitch variability"; "shimmer" is the corresponding variation in amplitude—our "amplitude variability"; others [19, 20, 24] have used slightly different ways of expressing essentially the same features. These measures reflect the "roughness" of the voice and are now widely accepted in acoustic waveform analysis. HNR and ANL are measures of the "breathiness" of the voice.

In this study there were differences in age, duration of airway placement, or both; these factors may influence vocal changes after surgery. However, we believe that the differences were too small to have any appreciable effect on the difference in vocal change between the two groups.

We have performed a large number of significance tests and therefore some of the apparently significant differences from baseline and between groups may be attributable to chance; however, it does seem clear that, overall, there was less change in vocal cord function with the LMA than with the tracheal tube.

Priebe, Henke and Hedley-White [1] found that the acoustic waveform obtained 2 days after tracheal extubation demonstrated a restoration towards normal speech and approximately 4 days elapsed before the waveform of normal phonation resumed. However, in our study, all variables had returned virtually to the preanaesthesia value at 24 h in both groups. We have no explanation for this difference between Priebe's results and our data.

Our data in the tube group are similar to those of Beckford and colleagues; they showed a statistically significant increase in cycle-to-cycle fundamental frequency variation in patients after intubation [2]. However, they did not demonstrate consistent changes in mucosal function with electroglottography or laryngeal endoscopy. Therefore, because phonation depends on both laryngeal and extralaryngeal factors, they suggested that postoperative vocal changes occurred as a result of multifactorial changes and were not caused solely by vocal fold trauma or vocal cord oedema. Our findings that the LMA caused statistically significant changes ($P = 0.046$) in HNR 4 h after extubation, with slight increases in PV and AV, may support the conclusion of Beckford's group, because the LMA would not be expected to damage the vocal cords directly.

Our results are consistent with those of Harris and colleagues [25], who also found significant differences in vocal effects produced by the LMA and the tracheal tube. However, in Harris and colleagues' study, the vocal changes produced by tracheal intubation were observed electroglottographically 18–24 h after surgery, while the vocal changes in our study, measured acoustically, resumed preanaesthesia values at 24 h in both groups. These differences reflect the different methods used for assessing vocal cord function.

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COMPARISON OF 0.125% BUPIVACAINE WITH 0.125% BUPIVACAINE AND CLONIDINE AS EXTRADURAL ANALGESIA IN THE FIRST STAGE OF LABOUR

M. E. O'MEARA AND T. GIN

SUMMARY

We have studied 42 healthy paturients with singleton vertex pregnancies, who were in the first stage of labour and requesting extradural analgesia. They were allocated randomly in a double-blind fashion to receive either 0.125% bupivacaine plain or 0.125% bupivacaine with clonidine 120 µg. Efficacy of analgesia was evaluated using linear visual analogue scoring (VAS), sensory block was assessed using bilateral pinprick in the mid-clavicular line and sedation scored on a five-point scale. Maternal and fetal cardiovascular variables were measured every 2 min for 20 min, at 30 min and subsequently at 15-min intervals. The reduction in VAS was greater at all times in the bupivacaine–clonidine group ($P < 0.01$*). The median (range) duration of analgesia was greater in the bupivacaine–clonidine group (114.5 (30–243) min) compared with the bupivacaine group (53 (30–100) min) (*$P < 0.001$*). Analgesia was associated with a reduction in arterial pressure in both groups, but there were no between-group differences. Maternal heart rate was less than baseline values at 30–90 min in the bupivacaine–clonidine group only. Sedation was greater in the bupivacaine–clonidine group, especially from 15 to 45 min (*$P < 0.01$*). There were no differences in fetal heart rate, mode of delivery or Apgar scores between the two groups. (*Br. J. Anaesth. 1993; **71**: 651–656)

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural. Anaesthetics, local: bupivacaine. Pharmacology: clonidine.

Bupivacaine is the standard agent for extradural analgesia in labour. Adrenaline and opioids are often added to improve analgesia, reduce the dose of bupivacaine and minimize side effects, but both additives have disadvantages. Adrenaline may contribute to fetal and maternal tachycardia and reduce spinal and uterine blood flow [1]. Fentanyl may cause pruritis, urinary retention, delayed gastric emptying [2], late respiratory depression [3] and reactivation of maternal herpes labialis [4].

Clonidine, an alpha$_2$ agonist, may be a useful adjuvant [5–7]. It has analgesic properties when administered extradurally alone [8] and acts synergistically with extradural opioids [9] and local anaesthetics [10]. Clonidine does not interfere with proprioception and does not cause motor block, nausea or vomiting. Respiratory depression does not occur [11], although ventilatory changes have been observed secondary to sedation when large doses of clonidine have been used [12].

Eisenach and colleagues suggested that clonidine may offer advantages as an analgesic in pregnancy [13]. It modulates, but does not abolish, sympathetic responses and so may interfere less with maintenance of arterial pressure during aortocaval compression [14]. Intrathecal and extradural clonidine have been studied extensively in the pregnant ewe and there were only minor changes in maternal and fetal physiology and biochemistry at concentrations of clonidine anticipated to be effective in the human [13, 15]. Extradural clonidine has been used successfully for analgesia after Caesarean section [12, 16, 17]. Oral clonidine has been used in pregnancy for the treatment of hypertension, with no adverse effects on the fetus [18, 19].

The aim of this study was to evaluate the safety and efficacy of a bolus of 0.125% bupivacaine 8 ml and clonidine 120 µg compared with 0.125% bupivacaine 8 ml alone for extradural anaesthesia in the first stage of labour.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee. We studied 42 pregnant patients with a singleton vertex pregnancy of at least 36 weeks gestation. They were in established labour but of less than 5 cm cervical dilatation, complaining of pain, using Entonox and requesting additional analgesia. All patients gave informed consent. We excluded patients younger than 18 yr, those with concomitant disease such as hypertension or diabetes, patients receiving antihypertensive drugs or tricyclic anti-

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depressants, those with a baseline heart rate less than 55 beat min^{-1} and patients who had already received opioid analgesia during this labour.

All patients were receiving continuous cardiotocograph (CTG) monitoring using an external transducer while arterial pressure was measured using a Dinamap on the non-dependent arm. Patients were given Hartmann's solution 500 ml i.v. over 10 min and positioned in the left lateral position. The extradural space was cannulated at L2–3 or L3–4 and 3 cm of catheter left in place. The patient was then repositioned to lie with a left lateral tilt. Baseline observations of maternal heart rate, arterial pressure, sedation, motor power and fetal heart rate were recorded. Pain was assessed by asking the patient to complete a 10-cm visual analogue scale (VAS) at the peak of a contraction. All patients received a test dose of 2 % lignocaine plain 3 ml and were allocated randomly to receive either 0.125 % bupivacaine 8 ml or 0.125 % bupivacaine 8 ml with clonidine 0.15 μg ml^{-1} (120 μg) 2 min after the test dose. One investigator prepared the extradural solution while the other blinded investigator assessed the patient.

Maternal heart rate, arterial pressure and fetal heart rate (FHR) were recorded at 2-min intervals for 20 min, at 30 min and thereafter at 15-min intervals. Hypotension was defined as a decrease in systolic arterial pressure of at least 20 %. It was treated by turning the patient to the left lateral position, administering 40 % oxygen by Hudson mask, giving Hartmann's solution 200 ml i.v. and ephedrine 6 mg, repeated as necessary.

The sensory level was assessed by response to bilateral pinprick at the mid clavicular line downwards every 2 min for 20 min, at 30 min and every 15 min thereafter. The patient was asked to complete a VAS at approximately 15-min intervals to coincide with the peak of a contraction. Onset of analgesia was assessed by the time to achieve sensory block of T12 and the time to reach the maximum decrease in VAS. Duration of analgesia was taken as the time from the initial dose to the time the patient requested additional analgesia. Unsatisfactory analgesia was defined as a request for further analgesia before 45 min or failure to achieve more than 50 % reduction in VAS.

Motor impairment was assessed at 15-min intervals using the Bromage scale. Sedation was assessed on a five-point scale (0 = wide awake; 1 = drowsy; 2 = dozing, eyes shut intermittently; 3 = asleep; 4 = unrousable) at 15-min intervals. Any episode of shivering during the first 30 min was noted.

The CTG was monitored continuously and analysed after delivery by an obstetrician who was blinded to the study drugs. Changes in the baseline FHR, beat-to-beat variability and the number of accelerations and decelerations were noted. The mode of delivery, neonatal birth weight and Apgar scores at 1 and 5 min were recorded. All patients were examined the next day.

Patient data were compared using Student's t test. Maternal arterial pressure, heart rate and FHR were analysed by repeated measures analysis of variance. The Mann–Whitney test was used to compare the time to sensory block of T12, time to maximum decrease in VAS, height of block, duration of block, sedation and VAS between groups. The baseline comparison of VAS used the raw data. Subsequent VAS were compared after transformation of data. Each VAS was divided by the baseline VAS for that patient to give values representing pain score as a fraction of the initial pain score. The incidence of successful analgesia, sedation and other categorical data were compared using the chi square test. $P < 0.05$ was considered significant.

RESULTS

There were 22 patients in the plain bupivacaine group and 20 in the bupivacaine–clonidine group. There were no differences between the groups in age, height, weight, parity or gestation (table I). The management of labour, duration of labour, and cervical dilatation before insertion of extradural catheters were similar also (table I).

TABLE I. *Patient data and details of labour (mean (range or* SD*) or number of patients)*

	Bupivacaine + clonidine	Bupivacaine
Age (yr)	26.2 (18–34)	28.0 (20–36)
Height (cm)	158 (5.2)	158 (4.4)
Weight (kg)	66.9 (11.4)	67.3 (6.7)
Gestation (weeks)	39.8 (1.3)	40 (1.4)
Parity = 0	18	15
Parity = 1	2	7
Artificial rupture of membranes	9	10
Oxytocin infusion	9	14
Cervical dilatation (cm)	2.4 (0.9)	2.6 (1.0)
Duration of labour before extradural (h)	4.2 (3.3)	4.8 (3.1)

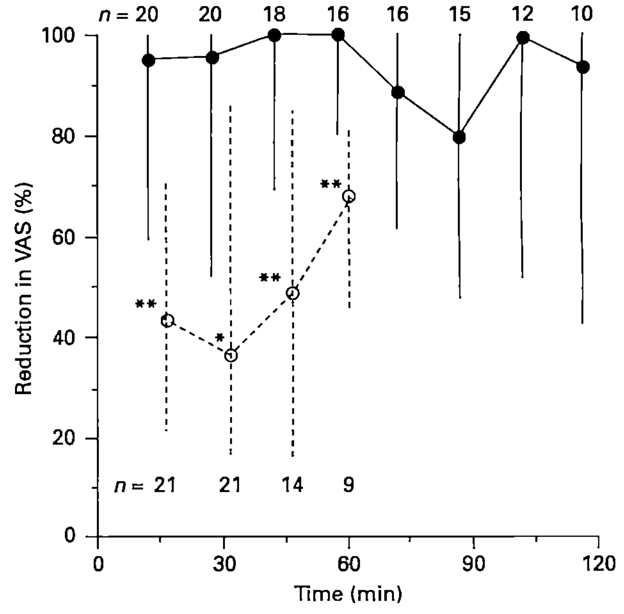

FIG. 1. Median and 25–75 % range for percentage reduction in visual analogue score (VAS) after extradural bupivacaine (○ — — ○) or bupivacaine and clonidine (●——●). Sample size at each time denoted by n. $*P < 0.05$; $**P < 0.01$ between groups.

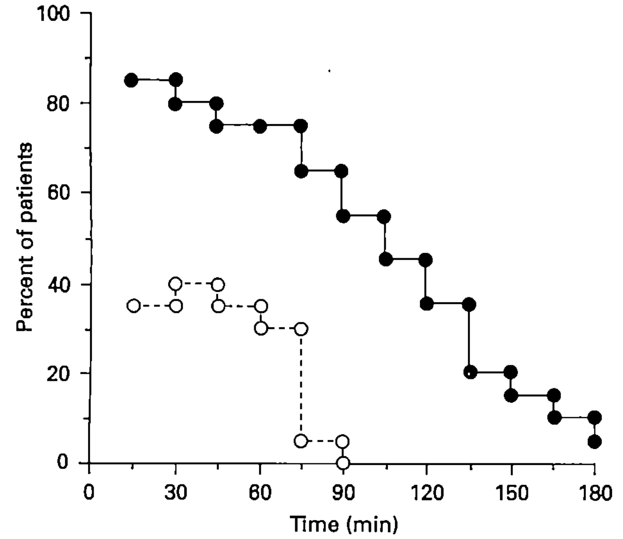

FIG. 2. Percentage of patients with at least 50 % reduction in pain score after extradural bupivacaine (○ — ○) or bupivacaine and clonidine (● —— ●).

TABLE II. *Quality and duration of analgesia (median (range) or number of patients)*

	Bupivacaine + clonidine	Bupivacaine
Unsatisfactory analgesia	3	12
Sensory block to at least T12	19	19
Onset to sensory block at T12 (min)	8 (4–30)	8 (2–18)
Maximum height of sensory block	T8 (T4–Nil)	T10 (T4–Nil)
Time to maximum analgesia (min)	15 (15–60)	15 (15–60)
Duration of analgesia (min)	114.5 (30–243)	53 (30–100)

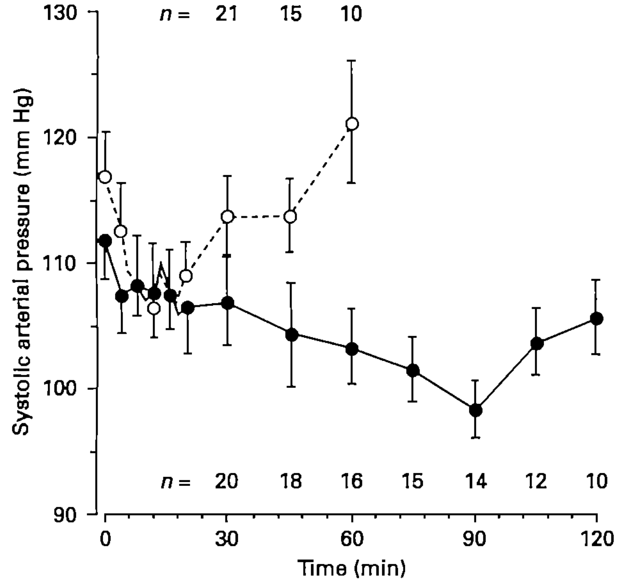

FIG. 3. Mean (SEM) systolic arterial pressure after extradural bupivacaine (○ --- ○) ($n = 21$) or bupivacaine and clonidine (● —— ●) ($n = 20$). Decrease in sample size at later times denoted by n.

There were incomplete data in two patients: the Dinamap printer was faulty for one patient and another patient declined to complete the VAS.

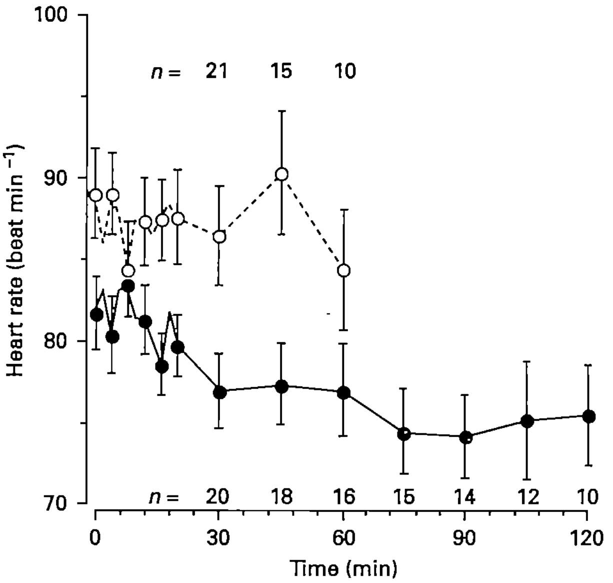

FIG. 4. Mean (SEM) heart rate after epidural bupivacaine (○ — ○) ($n = 21$) or bupivacaine and clonidine (● —— ●) ($n = 20$). Decrease in sample size at later times denoted by n.

Between-group comparisons of VAS and cardiovascular variables were made for the first 60 min only, because of the high exclusion rate in the bupivacaine group after that time, arising from requests for further analgesia.

There was no difference between groups in onset of sensory block to T12, maximal height of block, initial VAS or time to reach maximum reduction in VAS. The reduction in VAS from 15 to 60 min (fig. 1) and the maximal reduction in VAS were greater in the bupivacaine–clonidine group ($P < 0.01$). The number of patients with more than 50 % reduction in VAS was greater in the bupivacaine–clonidine group at all times (fig. 2). The mean duration of analgesia was twice as long in the bupivacaine–clonidine group ($P < 0.001$) (table II). Overall, analgesia was unsatisfactory in three (15 %) of the bupivacaine–clonidine group, compared with 12 (59 %) in the bupivacaine group ($P < 0.01$). These patients with failed analgesia were given 0.125 % bupivacaine 5–10 ml extradurally and this produced satisfactory analgesia in all of them.

There were no differences between groups in systolic (SAP), mean or diastolic arterial pressure initially or over the next 60 min. SAP in the bupivacaine group was less than baseline from 6 to 20 min ($P < 0.01$) (fig. 3). In the bupivacaine–clonidine group, SAP was less than baseline values from 16 to 90 min ($P < 0.01$). Hypotension occurred in three patients from the bupivacaine–clonidine group and two in the bupivacaine group. This was treated easily and ephedrine was effective in all patients. No patient required atropine.

Baseline heart rate was greater initially in the bupivacaine group but, after taking this into account, there were no differences between groups over the next 20 min (fig. 4). Heart rate was unchanged from baseline values in the bupivacaine group over the first 60 min. In the bupivacaine–clonidine group, heart rate was less than baseline values from 30 to 90 min ($P < 0.01$).

TABLE III. *Number of patients with sedation scores of 0 (awake), 1 (drowsy), 2 (dozing) and 3 (asleep), at 15-min intervals after extradural injection of drug*

	Time (min)							
Score	15	30	45	60	75	90	105	120
Bupivacaine + clonidine								
0	5	5	4	5	4	9	6	5
1	13	4	4	3	4	1	2	3
2	1	8	6	4	4	2	3	—
3	1	3	2	2	2	1	—	—
Bupivacaine								
0	18	16	10	7	3	1		
1	3	5	4	2	—	—		
2	1	1	1	—	—	—		

TABLE IV. *Neonatal outcome (number of neonates or mean (SD))*

	Bupivacaine + clonidine	Bupivacaine
Mode of delivery		
Spontaneous vaginal	8	7
Ventouse	9	5
Caesarean section	3	10
Apgar scores		
⩽ 7 at 1 min	4	3
⩽ 7 at 5 min	0	0
Birth weight (kg)	3.24 (0.43)	3.38 (0.45)

Sedation was greater in the bupivacaine–clonidine group from 15 to 60 min (table III). Fifty percent of these patients had a sedation score of 2 or greater at 30 min, but at no stage were patients unrousable. At 105 min, three of the 11 remaining patients had a score of 2.

Three patients in the bupivacaine–clonidine group and five in the bupivacaine group complained of shivering.

There were no differences in FHR between the groups and with respect to time. Detailed minute-by-minute analysis of the CTG was difficult because of the intermittently poor quality of many of the recordings as a result of movement and positioning of the external transducer. The different time course of analgesia for the two groups also made between-group comparisons difficult. Maternal hypotension was reflected usually by a transient decrease in the FHR. An overall impression of the significance of each CTG was made by the obstetrician. During the time of the study, no CTG showed any significant adverse events which required preparation for emergency delivery.

There were no differences in mode of delivery, Apgar scores or neonatal birth weight between groups (table IV). No maternal or neonatal complications were noted the next day.

DISCUSSION

The addition of clonidine to bupivacaine provided greater analgesia, but caused marked sedation. We used only 120 μg of clonidine (mean dose 1.84 $\mu g\ kg^{-1}$) in combination with a small dose of 0.125 % bupivacaine (8 ml). We chose this dose of clonidine because we wished to minimize the potential for cardiovascular side effects. We expected that this dose would be effective in labour, because clonidine has been shown in animal studies to be more effective against visceral pain than somatic pain, with reduced analgesic dose requirements in late pregnancy [20]. The degree of analgesia with 0.125 % bupivacaine 8 ml was comparable to that reported previously [21]. The duration of analgesia was relatively short, but an anaesthetist was present continually and the patient was able to request top-up administration at any time.

The improved quality of analgesia in the clonidine group at 15 min suggested the effect of clonidine was rapid. This has been noted previously [10]. Clonidine may have produced analgesia in a variety of ways. It may have central effects which modulate the descending pathways involved with nociceptive transmission. When administered extradurally alone, it is believed to produce analgesia predominantly by a spinal mechanism [22] from stimulation of the $alpha_2$ receptors of the dorsal horn. Clonidine may potentiate the effect of bupivacaine by reducing spinal cord blood flow and prolonging the effective availability of bupivacaine [7]. However, clonidine has a greater analgesic effect than that produced by the most powerful vasoconstrictors. Studies with extradural lignocaine and clonidine have indicated potentiation of analgesia and increased plasma concentrations of lignocaine, suggesting that clonidine may reduce hepatic metabolism of lignocaine [23]. There is no corresponding information for bupivacaine.

During pregnancy, there are increased concentrations of endogenous opioids [24] and clonidine may have potentiated their effects. Studies in animals have shown that clonidine enhanced pregnancy-induced analgesia may be antagonized by naloxone [20]. Other animal work suggests there is a morphine–clonidine interaction which is synergistic for visceral antinociception [25].

Recent studies of the analgesic effect of extradural clonidine have examined acute postoperative pain. The results varied depending on the site of operation, dose of clonidine and use of adjuncts. Eisenach, Lysak and Viscomi used clonidine alone and found that the large dose requirement (400–800 μg) resulted in unacceptable sedative side effects [26]. Gordh considered clonidine 150 μg inadequate for post-thoracotomy pain [27]. Carabine, Milligan and Moore studied patients who had undergone total hip replacement and found that a bolus of extradural clonidine alone and in combination with 0.25 % bupivacaine were superior to plain bupivacaine, and that combination therapy resulted in prolonged duration of action [10].

Some studies have shown that motor block is prolonged when clonidine is added to extradural lignocaine [22, 28] but not to bupivacaine [10]. We used a small dose of bupivacaine and few patients in each group developed motor block, so that possible potentiation of motor block could not be demonstrated.

The clonidine group were more sedated, but all could be roused to complete linear analogue scores. Sedation was of shorter duration than analgesia.

Clonidine is believed to act supraspinally, in particular at the locus coeruleus where there is a high concentration of alpha$_2$ receptors [29]. The onset of sedation was slower than the onset of analgesia, but more rapid than could be accounted for by cephalad spread in CSF. The systemic absorption of extradural clonidine is rapid, with peak plasma concentrations of clonidine occurring within 15 min of extradural administration [22, 30]. This is reflected in the relatively rapid onset of sedation in our patients. Some of the sedation may be a consequence of effective analgesia which allows the mother to rest. Neonatal sedation was not observed, but Apgar scores are insensitive measures of neonatal depression compared with neurobehavioural testing.

Five patients had significant hypotension which responded satisfactorily to ephedrine, while modest hypotension occurred with time in both groups. Although it appears that arterial pressure was decreased for a long time in the clonidine group, comparisons with the bupivacaine group should be restricted. Analgesia was more effective and longer lasting in the clonidine group, with the result that arterial pressure could be measured for a longer period. A decrease in arterial pressure may occur as a result of effective analgesia and all patients showed an increase in arterial pressure as pain returned.

The effects of extradural clonidine on cardiovascular variables are dose-related. It decreases arterial pressure and heart rate by enhancing parasympathetic nervous system activity and decreasing sympathetic nervous system activity at brainstem sites, and by inhibiting sympathetic outflow in the spinal cord. Clonidine has direct effects also on heart rate at the myocardium. With large doses, hypertension may occur secondary to stimulation of the alpha$_2$ postsynaptic vascular receptors.

There appeared to be no direct effects of clonidine on FHR and no episodes of maternal hypotension or bradycardia which could have resulted in an untoward outcome. FHR was measured continuously and the values at 2-min intervals analysed, but these values could be misleading as they gave no indication of beat-to-beat variability or other indicators of fetal distress. The CTG recordings were difficult to analyse subsequently and the use of fetal scalp electrodes and digital storage of FHR would have been preferable. Animal studies have shown a slowing of FHR with no evidence of fetal distress [13]. Reduced umbilical arterial flow occurred, but this was at concentrations of clonidine believed to induce hypoxaemia secondary to a platelet coagulation problem which is unique to sheep. Further studies in humans with Doppler measurement of umbilical artery flow would be valuable.

A single dose of clonidine was used and subsequent top-up doses were not standardized, so it is not possible to comment on the total dose requirements of bupivacaine. There were no differences between groups in the mode of delivery and the results were not inconsistent with obstetric practice in this hospital.

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CLONIDINE COMBINED WITH SUFENTANIL AND BUPIVACAINE WITH ADRENALINE FOR OBSTETRIC ANALGESIA

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SUMMARY

Clonidine produces analgesia via a non-opioid mechanism and it may be used as an interesting adjuvant to local anaesthetics and opioids in obstetric analgesia. To examine the effects of the addition of clonidine to bolus injections of bupivacaine, adrenaline and sufentanil, we enrolled 50 women receiving extradural analgesia for vaginal delivery into a double-blind study. They were allocated randomly to two groups: group A received a 10-ml extradural solution of bupivacaine 12.5 mg combined with adrenaline 25 µg and sufentanil 10 µg; group B received the same solution with clonidine 30 µg. Each patient was allowed two subsequent injections of the chosen solution. Subsequently, if still in the first stage of labour, analgesia was augmented with additional 10-ml injections of bupivacaine 12.5 mg with adrenaline 25 µg, without sufentanil or clonidine. The latter solution was used for perineal analgesia in group A; clonidine 30 µg was added in group B. During the first and second stages of labour, there was no difference between the two groups in duration of analgesia after the first injection (142 min in group A; 127 min in group B), number of injections (1.8 in group A; 1.9 in group B) and the total bupivacaine requirements (33.9 mg in group A; 34 mg in group B). The quality of analgesia was evaluated as very good in both groups (23/25 in group A; 24/25 in group B). The degree of motor block or the frequency of other side effects were not enhanced by clonidine. Analgesia was greater for episiotomy in group B (15/20 in group A; 21/21 in group B) ($P < 0.05$*). Within the limits of this study, the total dose of extradural clonidine 90 µg appeared to be safe for the mother and the child.* (Br. J. Anaesth. 1993; **71**: 657–660)

KEY WORDS

Anaesthetic techniques: extradural. Analgesics: sufentanil. Anaesthetics local: bupivacaine. Sympathetic nervous system: clonidine. Analgesia: obstetric.

Extradural analgesia for labour frequently comprises local anaesthetics in small concentrations (0.125% bupivacaine, or less) [1], with or without adrenaline and highly lipid-soluble opioids such as fentanyl [2] or sufentanil [3].

This use of opioids with small doses of local anaesthetics increases the quality and duration of analgesia and decreases the total amount of bupivacaine required [3, 4].

However, side effects such as nausea, pruritus and sedation still occur and, although the degree of motor block may be decreased, frequently it is still present at the last stage of labour.

Clonidine may be a useful adjuvant [5]: it produces analgesia via a non-opioid mechanism; unlike extradurally administered local anaesthetics, it does not interfere with proprioception and, unlike extradural opioids, it does not produce respiratory depression [6], nausea or pruritus. It enhances the analgesic potency of opioids and local anaesthetics without increasing the incidence of side effects [7].

The aim of our study was to see if the addition of a small dose of clonidine to a mixture of bupivacaine, sufentanil and adrenaline improved the duration of analgesia, reduced the number of injections or the total bupivacaine requirement and caused side effects in mother (motor block, pruritus, nausea, sedation) or child.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. After obtaining informed consent, we studied 50 women, ASA I or II, who were candidates for extradural analgesia for labour. Complicated pregnancies were excluded. Parity was not a selection criteria. The parturients were allocated randomly to two equal groups. An extradural catheter was inserted at either the L2–3 or L3–4 lumbar intervertebral space.

After a test dose of 2% lignocaine 2 ml with adrenaline 10 µg, an initial volume of 10 ml containing one of the following drug combinations was injected in a double-blind fashion (patients, anaesthetists, obstetricians and neonatologists were blinded to solutions):

Group A: bupivacaine 12.5 mg + adrenaline 25 µg + sufentanil 10 µg.

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Group B: bupivacaine 12.5 mg + adrenaline 25 µg + sufentanil 10 µg + clonidine 30 µg.

Five millilitre of the solution was injected with the patient on her left side and 5 ml, 10 min later, with the patient on the right side.

The patients were permitted a second injection of the same solution for any pain.

Subsequently, patients in both groups received further 10-ml injections of bupivacaine 12.5 mg + adrenaline 25 µg, without sufentanil or clonidine. For the entire first stage of labour, the mother lay on one side except for obstetric examinations, when she was in the supine position with left lateral tilt.

At full dilatation as judged by the obstetrician, perineal sensory block was tested by use of an ether swab to assess loss of temperature sensation (corresponding to Aδ and C fibre block) [8]. If anaesthesia was judged unsatisfactory, 10 ml of 0.125% bupivacaine with adrenaline 25 µg was injected in group A. The same mixture with clonidine 30 µg was given in group B with the patient in the sitting position.

We recorded the time when the injections were given, the duration of labour (first injection to delivery time) and the duration of analgesia provided by the first injection (interval between the first and the second injection).

Patient's evaluation of the efficacy of analgesia was reported on a verbal scale: very good (no or short periods of light pain); good (longer periods of pain, but still not disturbing); insufficient (permanent pain, dissatisfaction).

The evaluation of analgesia was repeated 30 min after each injection, at delivery and at the suture of episiotomy.

Haemodynamic monitoring of the mothers included non-invasive arterial pressure and heart rate, recorded every 5 min for 30 min after injections and every 15 min afterwards (Dinamap-Critikon, 1846 SX).

The degree of motor block was assessed on the Bromage scale: none, partial, almost complete, complete [9].

The frequency of all side effects including nausea, pruritus, sedation and urinary retention was recorded, and the mode of delivery (spontaneous, forceps or Caesarean section).

The fetus was monitored during labour by continuous tocometry (baseline fetal heart rate, variability, decelerations) (Hewlett-Packard 8040 A).

The Apgar scores of the newborns were noted by a neonatologist at 1, 5 and 10 min. The babies were assessed again 1 and 2 days after birth (general examination and Dubowitz score).

On the day after delivery, another anaesthetist questioned the mothers about their general evaluation of the pain relief during each stage of labour and episiotomy, their participation during expulsion (perception of the contractions, strength to push) and any side effects experienced during and after labour; they were discharged on day 6 after a general examination.

Means of independent variables were analysed by analysis of variance. Categorical variables were cross-tabulated. The statistical significance of relationships between cross-tabulated variables was based on Spearman R statistic. $P < 0.05$ was considered statistically significant.

RESULTS

Patients in the two groups were comparable in characteristics and labour variables (table I).

There was no difference in analgesia between the two groups, with a high incidence of very good pain relief in both groups: 23 of 25 patients in group A and 24 of 25 in group B for the two stages of labour; two patients in group A and one patient in group B had good analgesia for the first stage of labour; for the second stage, one in both groups had good pain relief and one in group A had insufficient pain relief.

Twenty-four patients in group A and 22 patients in group B required a last injection because of unsatisfactory perineal analgesia as assessed by cold swab.

Despite this supplementary perineal injection, five of 20 patients in group A found suture of episiotomy painful; all 21 group B mothers who underwent episiotomy were totally satisfied (table II).

The duration of labour, the number of injections and the total bupivacaine requirements did not differ between groups, but there was a slight decrease in hourly consumption of bupivacaine in group B.

The duration of analgesia after the first injection, in women who had received at least two injections during the first stage of labour, was not significantly modified by clonidine: 142 min in group A and 127 min in group B (table III).

The frequency of side effects was comparable in the two groups (table IV). Hypotension (decrease of more than 20% of the values before extradural injection) was treated first by fluids (four patients in each group) then, if persistent despite 500–1000 ml

TABLE I. *Patient data (mean (range or SD)). No significant differences between groups*

	Group A	Group B
Age (yr)	30.6 (21–42)	28.7 (20–40)
Weight at term (kg)	68.2 (10.8)	72.5 (14.6)
Weeks of pregnancy	39.4 (1)	39.3 (0.9)
Parity (median)	1	1
Primiparae	8	8
Multiparae	17	17
Induced labour	17	20
Cervical dilatation (median) (cm)	3	4

TABLE II. *Analgesia*

	n	Insufficient	Good	Very good	P
Dilatation					
Group A	25	0	2	23	0.56
Group B	25	0	1	24	
Expulsion					
Group A	25	1	1	23	0.54
Group B	25	0	1	24	
Episiotomy					
Group A	20	1	4	15	0.013
Group B	21	0	0	21	

TABLE III. *Bupivacaine requirements. * Calculated only for women who received a minimum of two injections for the first stage of labour. † Significant, but the result must be taken carefully because of wide variance*

	Group A	Group B	*P*
Duration of labour (min) (first injection–delivery time)	212 (130)	252 (131)	0.288
Total bupivacaine requirement (mg)	33.9 (10.9)	34 (12.7)	0.885
Dose of bupivacaine (mg h^{-1})	11.6 (4.6)	8.8 (2.3)	< 0.01†
Duration of analgesia with the first injection* (min)	142 (42)	127 (30)	0.371
Number of injections	1.8 (0.8)	1.9 (0.9)	0.652

TABLE IV. *Side effects. Hypotension = decrease of more than 20% of the values before the extradural injection*

	Group A	Group B
Hypotension		
Reversed by fluids (mean 1.12 litre per patient in each group)	4	4
Ephedrine required	1	1
Degree of sedation		
Acceptable	5	4
Excessive	0	1
Pruritus		
Mild	6	5
Excessive	0	1
Nausea/vomiting	2	1
Urine retention	1	3

TABLE V. *Motor block and participation of the mother*

	Group A	Group B
Motor block		
None	19	16
Partial	3	2
Almost complete	2	5
Complete	1	2
Unilateral motor block	2	4
Participation of the mother (subjective)		
None	2	3
Weak	2	3
Perfect	21	19
Instrumentation (forceps)	0	3

of fluids, by ephedrine 5–10 mg (one patient in each group). The degree of motor block did not differ between groups and the participation of the mother during the expulsion stage was excellent in 80% of the mothers; however, three deliveries required instrumental assistance (forceps) in group B (table V).

Two children (one in each group) presented with an Apgar score less than 8 at 1 min, but all the children recovered to an Apgar score greater than 8 at 5 and 10 min. There were no problems in the 24 h after birth.

DISCUSSION

Clonidine is a highly lipid soluble alpha$_2$ adrenergic agonist which acts via a non-opioid mechanism involving alpha$_2$ receptors at the dorsal horn [10–13]. When it is used alone, large doses are necessary to obtain pain relief, with hypotension and sedation in consequence [14–15]. However, combination with other drugs acting on different sites of the pain transmission pathways allows the dose of each component to be decreased: clonidine alone prolongs the sensory block of local anaesthetics and has a synergistic effect with extradural opioids [16–19]. When it is combined with another adrenergic agonist such as adrenaline, this prolonging effect on the spinal block of local anaesthetics is more marked. This effect does not depend on a local vasoconstriction, but is most probably produced by action on the descending adrenergic inhibitory system [20, 21].

During pregnancy, systemic clonidine is safe: doses in the range 150–900 µg have been shown to be safe for the treatment of pregnancy-induced hypertension [22]. It produces contractions of the human myometrium and uterine arteries *in vitro*, but does not increase the incidence of premature labour or the frequency of uterine contractions *in vivo*; it crosses the placental barrier easily, but no side effects have been described on the newborn during the neonatal period [23–26].

Extradural clonidine during pregnancy has been studied in a sheep model; a minor decrease in heart rate in ewes and fetus was noted, without changes in maternal and fetal blood pressure, intrauterine pressure or uterine blood flow [5].

For this first double-blind study, we chose a control solution known to be effective and used routinely in our institution (bupivacaine 12.5 mg with adrenaline and sufentanil 10 µg) [4, 27], to which a small dose of clonidine (3 × 30 µg maximum) was added. The bolus injection was preferred because it is used commonly in our unit, and the dose of clonidine 30 µg was chosen in accordance with our previous study [28].

Our experience confirmed the efficacy of the solution of 0.125% bupivacaine with adrenaline 25 µg and sufentanil 10 µg with 92% (23 of 25) of patients having very good analgesia during the two stages of labour.

We preferred to limit the total dose of clonidine to 90 µg to avoid possible side effects caused by cumulative doses of extradural clonidine. After the first two injections, no more clonidine was added to the solution. However, few patients would have been candidates for more than two injections: three in group A (one with three injections; two with four injections) and four in group B (one with three injections; three with four injections).

The addition of clonidine 30 µg did not improve the quality or the duration of analgesia; it did not decrease the number of injections for the first stage of labour; it produced a slight decrease in hourly bupivacaine requirement, which was statistically significant but must be interpreted with care because of the large variations between the two groups. This small difference has little clinical significance.

This apparent lack of benefit may be explained by several factors: the small dose of clonidine used in comparison with the relative large doses of bupivacaine and sufentanil and the pharmacokinetic properties of the two adjuvants, clonidine and sufentanil. Both clonidine and sufentanil are lipid soluble; they disappear quickly from the site of injection and diffuse into CSF and plasma. After a single extradural injection, the CSF concentration of clonidine increases to a maximum after 60 min and declines quickly with an elimination half-life of 1 h [29]. For sufentanil, the peak concentration appears earlier (within 30 min) and the elimination half-life is much longer (160 min) [30].

The quicker and longer action of an effective dose of sufentanil, such as 10 µg, could probably mask the effect of clonidine when injected at the same time in bolus injection. Continuous infusions of the same total hourly doses of clonidine and sufentanil should perhaps produce more constant analgesia and a greater decrease in bupivacaine requirements.

Analgesia for episiotomy, however, was very good in 15 of 20 patients in group A, and in all the patients (21) in group B. The three instrumental deliveries in group B reflect the same overall percentage of instrumental deliveries in our institution (12%).

There were no problems in our neonates. This is not surprising, as systemic (oral or i.v.) doses of more than 300 µg of clonidine have been shown to be safe [19].

In conclusion, within the limits of the present study, no side effects were seen with small doses of clonidine for obstetric analgesia in a group of 25 patients. Much larger numbers would be required to demonstrate the safety of the drug in wider application. The addition of small doses of clonidine in a bolus regimen of 30 µg with bupivacaine 12.5 mg with adrenaline and sufentanil 10 µg produced better analgesia for episiotomy, but this benefit appeared not to be of great clinical significance.

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COMPARISON OF THE ANALGESIC EFFECTS OF INTRATHECAL CLONIDINE AND INTRATHECAL MORPHINE AFTER SPINAL ANAESTHESIA IN PATIENTS UNDERGOING TOTAL HIP REPLACEMENT

D. J. FOGARTY, U. A. CARABINE AND K. R. MILLIGAN

SUMMARY

We have studied the anaesthetic and analgesic properties of intrathecal clonidine and intrathecal morphine in patients undergoing total hip replacement under spinal anaesthesia. After routine spinal anaesthesia with 0.5% plain bupivacaine 2.75 ml, patients were allocated randomly to receive intrathecal clonidine, morphine or saline (control) as adjuvant to the bupivacaine. Postoperative analgesic effects were measured by consumption of morphine via patient-controlled analgesia and visual analogue pain scores. Both intrathecal clonidine and intrathecal morphine prolonged the time to first analgesia compared with saline (mean 278 (SD 93.2) min, 498 (282.4) min and 54 (61.9) min, respectively) ($P < 0.001$). Total morphine consumption on the first night after operation was significantly less in the intrathecal morphine group. There were no differences between the clonidine and the control group. Intrathecal clonidine prolonged the duration of spinal analgesia, but was markedly inferior to the intrathecal morphine in providing subsequent postoperative analgesia. (Br. J. Anaesth. 1993; **71**: 661–664)

KEY WORDS

Anaesthetic techniques: spinal. Analgesics: morphine. Anaesthetics local: bupivacaine. Pharmacology: clonidine.

Both opioids [1, 2] and alpha$_2$ agonists [3–5] have been shown to produce analgesia when administered spinally. Adjuvant drugs may be added to the local anaesthetic solution, not only to prolong the duration of the block, but also to provide postoperative spinal analgesia.

Clonidine, an alpha$_2$ agonist, has been shown to prolong spinal anaesthesia, but there are few data on its analgesic properties when used as an adjuvant to intrathecal bupivacaine.

PATIENTS AND METHODS

After obtaining Ethics Committee approval and informed consent, we studied 90 healthy (ASA I–II) patients presenting for elective total hip replacement. Patients were not receiving any cardiovascular medication and they were excluded if receiving any drug other than simple oral analgesics. During the preoperative visit, the patients were shown a 10-cm visual analogue scale with the two extremes no pain and the worst possible pain. The use of a patient-controlled analgesic system (PCAS) was explained. Patients were premedicated with temazepam 20 mg 60–90 min before induction of anaesthesia.

Two i.v. cannulae were inserted: one for i.v. fluids and the other for postoperative PCAS. Spinal anaesthesia was induced with the patient in the lateral position: 0.5% plain bupivacaine 2.75 ml was administered over 10 s at the L3–4 interspace. Patients were then allocated randomly to one of three groups to receive 0.9% saline 1 ml, clonidine 75 μg (50–75 kg) or 100 μg (76 kg or more) or morphine 1 mg. Clonidine and morphine were diluted to 1 ml with 0.9% saline. All patients received a total injectate of 3.75 ml.

The anaesthetist administering the spinal drugs played no further part in the subsequent assessment of the patients. Neither the patients nor the observers were aware of which drug had been administered.

Monitoring consisted of non-invasive arterial pressure, ECG, pulse oximetry and ventilatory frequency. All patients received oxygen by face mask, droperidol 2.5 mg i.m. for prophylaxis against emetic sequelae and cefamandole 2 g i.v. as antibiotic prophylaxis. Patients were sedated with an infusion of propofol, initially 3 mg kg^{-1} h^{-1} which was continued until skin closure. Hypotension (defined as a

TABLE I. *Mean (range or SD) age, weight, height and sex distribution of patients. No significant differences between groups*

	Saline	Clonidine	Morphine
Age (yr)	61 (45–83)	68 (53–80)	66 (44–78)
Weight (kg)	69 (13.7)	68 (11.8)	72 (9.1)
Height (cm)	165 (12.5)	165 (9.6)	166 (10.4)
Sex (M/F)	18/12	20/10	17/13

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TABLE II. *Operative details (mean (SD)). No significant differences between groups*

	Saline	Clonidine	Morphine
Duration of surgery (min)	81 (11.8)	85 (15.3)	92 (13.65)
Blood loss (ml)	1095 (555.9)	1034 (502.5)	1262 (558.6)
Haemoglobin concn (g dl^{-1})			
Before op.	13 (1.2)	12 (2.8)	12 (3.7)
After op.	11 (1.6)	11 (1.5)	12 (1.3)

reduction in systolic pressure of more than 30% of the preinduction value) was treated with ephedrine 5 mg i.v.; bradycardia of less than 50 beat min^{-1} was treated with atropine 0.6 mg i.v. I.v. fluid therapy consisted of Dextran 70 0.5 litre followed by Hartmann's solution 250 ml h^{-1} during operation and 0.18% saline in 4% glucose 100 ml h^{-1} after operation. Blood was transfused when blood loss exceeded 20% of the patient's estimated blood volume.

After operation, patients were transferred to a high dependency unit where ECG and pulse oximetry were recorded continuously and arterial pressure was measured at 15-min intervals for the first 2 h and at 30-min intervals thereafter for 24 h. Pain scores were recorded at 2-hourly intervals. Motor block and sensory level were recorded at 15-min intervals until they had regressed below the level of L4. Each patient was provided with a PCAS (Abbott, Lifecare) set to deliver morphine 1 mg with a 5-min lockout. The PCAS memory enabled a record of all pump operations to be retrieved.

Patients were assessed for urinary retention, nausea, vomiting, pruritus, headache and backache. Total blood loss, fluid balance and postoperative haemoglobin concentrations were recorded also.

Data were analysed statistically by analysis of variance (ANOVA), Mann–Whitney *U* test, Student's *t* test and chi-square test where appropriate. Significance was set at the 5% level ($P < 0.05$).

RESULTS

Surgery and assessment were completed successfully in all patients. Patients groups were similar in age, weight, height and sex distribution (table I).

There were no significant differences between the groups in duration of surgery, total blood loss, preoperative and postoperative haemoglobin concentration and fluid balance (table II).

There were no significant differences between the groups in the intraoperative mean arterial pressures. The number of patients requiring ephedrine was similar for all groups (clonidine 17, morphine 16 and saline 11), as was the amount of ephedrine used (table III).

The time taken for regression of the anaesthetic block to the L4 dermatome was significantly greater in the clonidine group compared with the saline and morphine groups (table IV). The time from the end of surgery until the first request for analgesia was significantly greater for both the clonidine and the morphine groups compared with the saline group.

The total morphine used and the mean morphine consumption rate over the recovery period were similar in the saline and clonidine groups, but significantly less in the morphine group ($P < 0.05$) (fig. 1).

TABLE III. *Utilization of ephedrine: number of patients and mean (SD) dosage*

	Saline	Clonidine	Morphine
No. (%) patients requiring ephedrine	11/30 (37%)	17/30 (57%)	16/30 (53%)
Ephedrine dose (mg)	4.4 (6.37)	5.50 (7.71)	7.8 (10.23)

TABLE IV. *Analgesic data (mean (SD)). Significant differences (P < 0.05): * compared with two other groups; † compared with saline group*

	Saline	Clonidine	Morphine
Time to regress below L4 (min)	138 (59.9)	216 (97.1)*	109 (57.8)
Time to first analgesia (min)	153 (61.9)	278 (93.2)†	497 (282.3)*
Total morphine used (mg)	31 (18.7)	27.9 (13.1)	5.5 (6.7)*
Morphine consumption (mg h^{-1})	1.6 (1.1)	1.5 (0.63)	0.3 (0.36)*

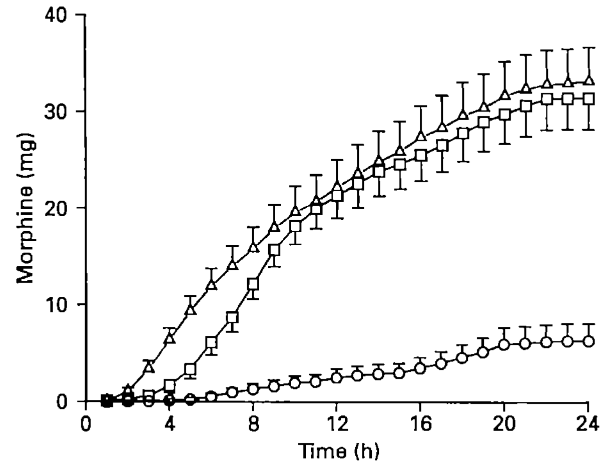

FIG. 1. Mean (SEM) postoperative cumulative morphine consumption after intrathecal saline (△), clonidine (□) or morphine (○).

Visual analogue scores for analgesia were significantly better in the morphine group at 2, 4, 6, 8, 10 and 12 h after operation compared with the saline controls and significantly better than the clonidine group from 4 to 10 h. Clonidine analgesia was significantly better than saline at 2 h and 4 h. The following morning, the saline group had significantly smaller pain scores than the two other groups (table V).

TABLE V. Mean (SD) postoperative visual analogue scores. Significant differences compared with saline: *P < 0.05; **P < 0.01; ***P < 0.001. Significant differences compared with clonidine: ††P < 0.01; †††P < 0.001

Time	VAS (mm) Saline	Clonidine	Morphine
2 h	8.7 (14.67)	1.6 (4.53)*	1.0 (1.94)**
4 h	27.3 (23.02)	9.5 (18.56)***	1.8 (5.53)***††
6 h	24.7 (26.26)	13.2 (15.53)	1.7 (2.63)***†††
8 h	14.2 (19.70)	13.9 (17.53)	2.6 (4.87)*††
10 h	11.6 (18.41)	9.5 (10.97)	1.8 (2.87)**††
12 h	12.2 (15.52)	7.3 (11.96)	1.7 (2.10)***
08:00	0.5 (2.03)	7.1 (13.93)*	3.1 (5.63)*

TABLE VI. *Incidence of postoperative sequelae*

	Saline	Clonidine	Morphine
Nausea	13 (43%)	7 (23%)	12 (40%)
Vomited	8 (26%)	11 (36%)	6 (20%)
Pruritus	1 (3%)	1 (3%)	5 (15%)
Headache	0 (0%)	1 (3%)	0 (0%)
Dry mouth	17 (56%)	12 (40%)	8 (26%)

There were no significant differences between the groups in postoperative side effects (table VI).

DISCUSSION

Many workers have attempted to prolong the effect of spinal anaesthesia and provide postoperative analgesia with the use of adjuvant drugs. Diamorphine and morphine are used commonly for this purpose [1, 2]. Opioids produce prolonged analgesia after a single dose, but are associated with side effects, notably delayed respiratory depression, nausea and vomiting, urinary retention and pruritus.

Although the endorphin system is well recognized, there are many other mechanisms involved in spinal antinociception and alpha$_2$ adrenergic agonists such as clonidine, calcitonin, adenosine and somatostatin have been shown to possess spinally-mediated analgesic properties [7–9].

The alpha$_2$ adrenergic agonists produce antinociception by mimicking the post-synaptic actions of noradrenaline, released from bulbospinal pathways. Alpha$_2$ adrenergic binding sites are situated pre- and post-synaptically to small primary afferents in the dorsal horn. Local administration of alpha$_2$ adrenergic agonists depresses the activity of wide dynamic range neurones in the dorsal horn and depresses the release of substance P [10, 11]. It has been shown also that alpha$_2$ adrenoreceptor agonists have spinal analgesic properties [3–6].

Vasopressors, such as adrenaline, have been shown to prolong spinal anaesthesia [12–14] and Racle and colleagues [14] have shown that clonidine 150 μg potentiates the motor and sensory effects of isobaric spinal anaesthesia more than adrenaline. This led to speculation that the mechanism of action of clonidine was local vasoconstriction at spinal cord level. Although clonidine may alter spinal blood flow in a dose-dependent manner [15], this is unlikely to be the only mechanism of action, as there is evidence for analgesic effects of intrathecal clonidine from other workers [5].

There are few data on the comparative postoperative analgesic effect of clonidine compared with conventional intrathecal opioids. The purpose of this study was to examine the analgesic effects of intrathecal clonidine compared with intrathecal morphine using PCA and visual analogue scores. In an earlier dose–response study [16], effective analgesia was demonstrated using extradural doses of clonidine in the range 3–10 μg kg^{-1}, although hypotension and sedation were side effects. For the purpose of this study, a smaller dose of clonidine was chosen in view of the route of administration and in an attempt to limit the extent of any hypotension. We limited our dose of clonidine to 100 μg in this age group to minimize intraoperative cardiovascular side effects. Spinal cord toxicity has not been demonstrated with the use of intrathecal clonidine [17].

We found that intrathecal clonidine prolonged the effect of spinal anaesthesia, in terms of both the time to regression of the block and the time until the first request for analgesia. After operation, when analgesia was first requested in the clonidine group, patients demanded frequent doses of morphine to achieve adequate analgesia. There was no evidence of any residual analgesia. VAS in the morphine group were significantly smaller from 4 to 12 h after operation, while clonidine analgesia was greater than that of saline, but only for the first 4 h—that is, during the time of prolonged spinal block. By the next morning, pain scores in all groups were small, but saline scores were significantly less than those in the two other groups, presumably because of the greater utilization of morphine.

Side effects were similar in all groups. Nausea and vomiting were surprisingly prevalent, even in the non-intrathecal opioid groups, possibly as a result of the emetic effect of morphine. Jacobson, Kokri and Pridie have demonstrated no difference in postoperative nausea between intrathecal and PCAS morphine [18].

Cardiovascular stability is an obvious concern with spinal anaesthesia, especially when intrathecal clonidine is used. Despite the high incidence of use of ephedrine in all three groups (37%, 57%, 53%), there was no statistical difference. We feel that the intraoperative ephedrine had no effect on the postoperative analgesia in the three groups.

It would seem from our data that the addition of intrathecal clonidine 75–100 μg conferred little advantage in terms of postoperative analgesia. There was a significant increase in duration of bupivacaine spinal block and time to first analgesia, but no evidence of any residual analgesic effect and no advantage in terms of analgesia and postoperative side effects.

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SINGLE-DOSE, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY CROSS-OVER COMPARISON OF EXTRADURAL AND I.V. CLONIDINE IN CHRONIC PAIN

D. CARROLL, A. JADAD, V. KING, P. WIFFEN, C. GLYNN AND H. McQUAY

SUMMARY

We studied 10 patients with chronic back pain who had claimed benefit with a previous extradural dose of clonidine 150 µg combined with local anaesthetic. We compared a single dose of clonidine 150 µg given by either the extradural or i.v. route in a double-blind, randomized, double-dummy and cross-over fashion, with 80% power to detect a difference in the analgesic effect of the two routes. Pain intensity, pain relief, adverse effects, mood, sedation and vital signs were assessed by a nurse observer. I.v. clonidine produced significantly ($P < 0.04$*) greater analgesia than extradural clonidine in one of the five analgesic outcome measures. Clonidine given by either route produced statistically significant sedation and significant decreases in arterial pressure and heart rate. In this study, extradural clonidine had no significant clinical advantages compared with i.v. clonidine; clonidine 150 µg by either route produced a high incidence of adverse effects.* (Br. J. Anaesth. 1993; **71**: 665–669)

KEY WORDS

Anaesthetic techniques: extradural. Sympathetic nervous system: clonidine.

The clinical role of clonidine and other $alpha_2$ adrenergic agonists in pain management remains unresolved. Despite the considerable clinical use of clonidine over the past 10 years, there is little evidence from randomized controlled trials to demonstrate its analgesic efficacy when given alone, and the adverse effects with which it is associated may severely limit its usefulness.

The first suggestion of the analgesic effects of clonidine given extradurally in neuropathic pain was reported by Tamsen and Gordh [1]. Since then, several studies have examined the extradural route of administration using both bolus doses [2, 3] and infusions [4]. Several studies showed that clonidine extended the duration of local anaesthesia [5–9] and that it enhanced opioid analgesia in both animals [10–12] and man [13, 14]. There is some evidence of a dose-related response for adverse effects with clonidine [4], but not for analgesic effects [4, 15]. Other routes studied include oral [16], i.v. [17] and transdermal [15]. The placebo-controlled studies available currently in either acute or chronic pain are inconclusive because of conflicting results [2, 6, 16, 18]. The suggestion that clonidine may be effective in neuropathic chronic pain was supported by the finding that some patients had better analgesia with extradural clonidine than with extradural morphine [19].

The aim of this study was to compare the analgesic efficacy and adverse effect profile of i.v. clonidine with extradural clonidine using a double-blind, randomized cross-over design in patients with chronic pain. Negative control (placebo) studies with this class of drugs are subject to methodological problems, primarily because of the presence of overt adverse effects, such as hypotension and sedation. These adverse effects lead to difficulties in maintaining the double-blinding [16, 20]. Positive control studies, using different doses or routes of administration of the test drug, may therefore provide a useful alternative for this class of drug [20], because a similar pattern of adverse effects occurs in all treatment groups, so that analgesic effects can be determined in a more genuinely double-blind way.

PATIENTS AND METHODS

Ethics Committee approval was obtained to recruit patients with chronic back pain attending the Oxford Regional Pain Relief Unit for this single dose, double-blind, double-dummy randomized cross-over study. Patients were selected only if they had constant reproducible pain of moderate or severe intensity below the umbilical region, and if they had previously reported pain relief from an open treatment with extradural clonidine 150 µg combined with local anaesthetic.

Patients were admitted to hospital the day before the study, and after clinical examination a judgement was made as to whether the pain was nociceptive, neuropathic or idiopathic [21]. An extradural catheter was inserted between L2 and L4, using a

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standardized aseptic technique. A test dose of 2% lignocaine 5 ml was given and the position of the catheter confirmed by evidence of sensory or motor block, or both. All clinical examinations and procedures were performed by one investigator (A. J.) assisted by the same nurse (V. K.).

The study began the day after the extradural catheter had been inserted, at least 12 h after the test bolus dose. The study was started only if the pain had returned to baseline intensity, if there was no evidence of residual block and if the pain was of at least moderate pain intensity (categorical pain intensity scale).

Patients received a single dose of clonidine i.v. or extradurally on two separate occasions in randomized order. Treatments were double-blind and double-dummy: on each occasion patients received both an extradural and an i.v. injection, placebo or active. All study treatments were injected over 1 min by the same investigator (A. J.) giving the extradural bolus first. Patients were assessed by one nurse observer (D. C.), using the standard techniques described below. The investigator, nurse observer and patient were not aware of which treatment had been given at any time. Treatments were separated by at least 24 h and the next treatment was given only when the effects of the first had worn off and the pain had returned to baseline intensity. Patients remained in bed throughout each 6-h study period.

At the end of the 6-h study period, patients were free to get out of bed if they were judged to be fully recovered. If they still had pain relief from the study treatment, the time when the pain returned to its normal intensity was recorded. The next morning, patients were reassessed and received the second study treatment, in a manner identical to the first. If patients were still obtaining pain relief after the first treatment, the catheter was removed, they were discharged home and they were asked to return for the second study treatment when the pain had returned to its baseline intensity. This second treatment was then given following the same procedure as the first.

Study treatments and randomization codes were prepared and supplied by the Pharmacy Department at the Churchill Hospital. All treatments were prepared on the day of the study, under aseptic conditions. Treatments were presented as two, prefilled 10-ml syringes, identified only by patient name, study number (1–10), route of administration (i.v. or extradural) and occasion (1 or 2). The treatment code was kept in the pharmacy in a sealed envelope which was opened after the study was completed. Patients received two single-dose injections, extradural and i.v. on two separate occasions, of clonidine 150 μg (Catapres, Boehringer Ingelheim) or placebo (normal saline).

Assessments

Before study treatment. Baseline assessments were made for current pain using a categorical verbal rating scale for pain intensity (severe = 3; moderate = 2; mild = 1; no pain = 0), by an eight-word scale (Tursky scale; randomly placed words ranging from "no pain" to "excruciating", scored 0–7) and by a visual analogue scale of pain intensity (VASPI: 100-mm line labelled "no pain" at one end and "the worst possible pain" at the other end). Mood was measured with a visual analogue scale (VASMOOD: 100-mm line labelled "worst I could feel" at one end and "the best I could feel" at the other end). Sedation was measured with a categorical scale (asleep = 3; moderately drowsy = 2; mildly drowsy 1; alert = 0). If patients were sleeping then they were woken at each assessment time. Heart rate, arterial pressure and oxygen saturation of arterial blood were measured (Hewlett–Packard GMBH 78352C).

After study treatment. Pain intensity, mood, sedation and vital sign measurements were repeated at 30, 60, 90, 120, 240 and 360 min after the end of the i.v. and extradural injections. Pain relief was also assessed at these times using a categorical verbal rating scale (none = 0; slight = 1; moderate = 2; good = 3; complete = 4) and a visual analogue scale (VASPR: 100-mm line labelled "no relief" at one end and "complete pain relief" at the other). Observed and volunteered adverse effects were recorded. Patients were asked "is there anything else bothering you, or has the treatment upset you in any way?"

At the end of the study, both the patient and the nurse made an overall global rating of the treatment. Patients were asked "how effective was the treatment today?". This was rated as poor = 0; fair = 1; good = 2; very good = 3; excellent = 4. The nurse made her rating before the patient, to avoid bias. After the second study period, patients were asked which treatment they preferred "1 or 2?".

Statistical analysis

It was estimated that at least 10 patients would be necessary to achieve power of 80% with alpha level of 0.05 (two-tailed) and beta level of 0.2 to detect a difference of 40% between the two routes of administration on the primary outcome measure, TOTPAR.

The sum of the pain intensity difference from the categorical pain intensity scale, the visual analogue for pain intensity and the Tursky 8 word score were calculated [22] to derive SPID, VASSPID and WORDSPID, respectively. Total pain relief was calculated from the categorical scale for pain relief (TOTPAR) and from the visual analogue scale for pain relief (VASTOTPAR). The area under the curve for mood against time (AUCMOOD) was calculated.

Comparisons were tested using the Wilcoxon rank test and were considered statistically significant if $P < 0.05$. Results are presented as median and range.

RESULTS

The study took place between December 1991 and February 1992. Ten patients were studied (table I). Patient No. 4 had pain at two separate sites; these were assessed independently. Results are therefore presented for 11 pain sites. All patients received both of the study treatments and no patient withdrew from the study. Two of the patients had relief

TABLE I. *Patient details*

No.	Age (yr)	Sex	Diagnosis	Site	Duration (months)	Character
1	51	M	Arachnoiditis	Back and leg	306	Neuropathic
2	40	F	Arachnoiditis	Back and leg	120	Neuropathic
3	77	M	Paraparesis	Back	360	Neuropathic
4	55	M	Arachnoiditis	Back and leg	23	Neuropathic
5	66	F	Arachnoiditis	Leg	480	Neuropathic
6	50	M	Arachnoiditis	Leg	264	Nociceptive
7	70	F	Osteoarthritis spine	Leg	240	Nociceptive
8	58	M	Myelopathy	Back	24	Neuropathic
9	42	M	Idiopathic back pain	Back	6	Idiopathic
10	59	M	Arachnoiditis	Leg	30	Neuropathic
Median	57				180	
Range	40–77				6–480	

TABLE II. *Analgesia scores (mean (range)) (10 patients—11 pain sites). * Significant difference between routes (Wilcoxon Test). † Two patients could not distinguish the treatments*

	Extradural		I.v.
SPID	3 (−2.5 to 6)		2 (−1 to 10)
TOTPAR	4 (0–14.5)		6 (0–16)
VASSPID	58 (−54 to 300)		117 (−43 to 323)
VASTOTPAR	60 (0–416)		58 (0–428)
WORDSPID	0 (−6 to 9)	*	2 (−3 to 16)
AUCMOOD	−6 (−328 to 48)		−56 (−267 to 164)
Patient global	0 (0–2)		1 (0–2)
Nurse global	0 (0–1)		1 (0–2)
Treatment preferred†	5		3

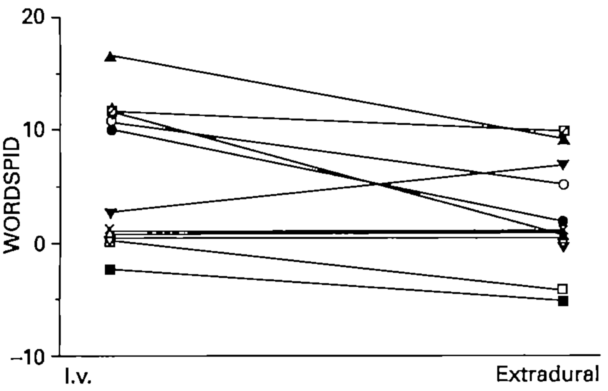

FIG. 1. Individual WORDSPID scores for the 10 patients (11 pain sites) after i.v. clonidine 150 µg or extradural clonidine 150 µg. Three patients had WORDSPID scores of 0 on both occasions.

beyond the 6-h study period: patient No. 1 reported relief for 16 days after the extradural treatment and 9 days from the i.v. treatment and patient No. 3 had relief for 56 days after the extradural treatment. Both patients received the second treatment as soon as the pain relief from the first treatment wore off.

There were no significant differences between the treatments for SPID, TOTPAR, VASSPID and VASTOTPAR. There was, however, a statistically significant difference for WORDSPID ($P = 0.036$, Wilcoxon). Overall, the pain relief and pain intensity reduction scores were greater for the i.v. dose (table II, fig. 1); the difference was statistically significant only for WORDSPID.

AUCMOOD scores were small for both treatments, with no significant difference between the routes. The global ratings by both the patient and the nurse were poor, with no significant difference between routes. Two patients could not distinguish between relief obtained from the two treatments; three preferred the i.v. clonidine and five preferred the extradural dose.

There was a significant increase from baseline in the mean sedation scores for clonidine by both routes: at 60, 90, 120 and 180 min for the extradural route and at 30, 60, 90, 120 and 180 min for i.v. administration. The maximum change (from alert at baseline to moderately drowsy) occurred at 90 min for both routes. There was no significant difference between the routes.

There was no significant change in mean oxygen saturation scores from baseline for clonidine by each route, but a significant decrease in heart rate with extradural clonidine at 60, 90, 120, 180, 240, 300 and 360 min and with i.v. clonidine at 90, 120 and 360 min. Maximum change (18% difference from mean baseline) was at 90 min after extradural clonidine and at 120 min after i.v. administration. There was no significant difference between the routes. There was a significant decrease in the mean systolic and diastolic arterial pressures at all assessment times for both treatments. Maximum change (20% difference from mean baseline) was at 90 min for both routes. There was no significant difference between the routes.

Adverse effects

The incidence of adverse effects was high for both treatments. Eight patients experienced adverse effects from extradural clonidine and seven from i.v. clonidine. Seven patients had adverse effects with clonidine by both routes (patients Nos 1, 2, 3, 4, 5, 8, 10); two patients had no adverse effects from either route (patients Nos 7 and 9) and one patient had adverse effects from the extradural route only (patient No. 6). Only one patient reported the adverse effects to be unacceptable, and did so for both treatments (patient No. 5). Three patients had more than one adverse effect after extradural clonidine (patients Nos 2, 3, 9) and three patients had more than one adverse effect after i.v. clonidine (patients Nos 4, 5, 10).

Adverse effects occurred earlier with i.v. (30 min) than with extradural. The most common adverse effect was dry mouth, affecting seven patients for both routes. Other adverse effects were headache, feeling hot, dizziness, sweating and shaking. In those patients who were affected, many of the effects were continuous and persisted throughout the study.

DISCUSSION

This study suggests that there is no advantage to be gained by giving clonidine by the extradural route compared with giving it by the i.v. route. Although only 10 patients were studied, the methods were sufficiently sensitive to detect a significant difference in one measure of analgesia—i.v. clonidine gave greater analgesia than extradural clonidine. A similar trend was seen with the other measures.

Similar results have been reported in postoperative pain—an i.m. dose of clonidine was indistinguishable from an extradural dose in a parallel group design [23]. This is analogous with the finding that there was no clinical advantage with extradural fentanyl compared with the same dose given by the i.v. route [24, 25].

The finding of no clinical advantage for extradural clonidine over parenteral clonidine in postoperative pain, taken with our results from chronic pain patients, raises at least two points. First, the pain relief which resulted from clonidine by each route in this study was poor (fig. 1). It might be argued that the dose of clonidine (150 µg) was insufficient to produce effective analgesia. However, this dose did produce adverse effects, suggesting that, if larger doses were to be found to produce better analgesia, the associated adverse effects would nevertheless preclude the use of the drug. Second, if extradural clonidine does not have any analgesic advantage over the same dose given parenterally, why is extradural rather than i.v. clonidine being used?

Such considerations would argue against the use of clonidine as the sole analgesic in postoperative pain. Similarly, for chronic pain patients, single doses of extradural clonidine alone do not appear to produce lasting benefit. Although in this study patients were selected because of claimed benefit from a previous open dose of extradural clonidine combined with local anaesthetic, in all but two the pain had returned to baseline after extradural clonidine alone within 24 h. There may nevertheless be a role for clonidine in combination with a local anaesthetic agent or opioid, or both, because of known synergism between them [26].

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COMPARISON OF PATIENT-CONTROLLED ANALGESIA WITH AND WITHOUT A BACKGROUND INFUSION AFTER LOWER ABDOMINAL SURGERY IN CHILDREN

E. DOYLE, D. ROBINSON AND N. S. MORTON

SUMMARY

Forty children aged 6–12 yr undergoing appendicectomy were allocated randomly to receive postoperative i.v. morphine by a patient-controlled analgesia (PCA) system (bolus dose 20 $\mu g\ kg^{-1}$ with a lockout interval of 5 min) or the same PCA with a background infusion of morphine 20 $\mu g\ kg^{-1}\ h^{-1}$. Patients breathed air and oxygen saturation was monitored by continuous pulse oximetry. Scores for pain, sedation and nausea were recorded hourly. Patients with PCA + background infusion received significantly more morphine than those with PCA only. Both groups self-administered similar amounts of morphine using the PCA machine. There were no significant differences in the pain scores of the two groups. Patients with PCA + background infusion suffered more nausea ($P < 0.01$), more sedation ($P < 0.05$) and hypoxaemia ($P < 0.001$) than those with PCA only. They also had a better sleep pattern than those with PCA only. (Br. J. Anaesth. 1993; **71**: 670–673).

KEY WORDS

Analgesia: postoperative, patient-controlled. Analgesics: morphine. Anaesthesia: paediatric.

Patient-controlled analgesia (PCA) has been used in children since 1987 [1], initially in adolescents and later in selected children as young as 5 yr [2–6]. The drug used most commonly has been morphine with a bolus dose of 10–25 $\mu g\ kg^{-1}$ and a lockout interval of 5–15 min. A continuous background infusion has been used in some studies. These studies were empirical and there are few which have compared different PCA regimens in paediatric practice.

The addition of a background infusion to PCA may improve the quality of analgesia provided [7] by reducing the decrease in plasma concentrations of opioid during sleep. However, a fixed infusion may reduce the inherent safety of PCA by continuing to deliver opioid to a patient who has adequate analgesia [8]. The use of a background infusion may also result in larger amounts of opioid being administered and an increase in the incidence of opioid-induced side effects [9].

This study was carried out to assess the effect on postoperative analgesia, sedation, ventilatory frequency, nausea and vomiting, sleeping pattern and arterial oxygen saturation (Sp_{O_2}) of adding a background infusion of morphine to a PCA regimen in children.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained. We studied 40 children aged 6–12 yr undergoing appendicectomy. The patients were visited before operation when the principles of using PCA were explained to the child and parents, and the patients were taught how to use the trigger of the PCA machine.

Patients were studied only if they had not received preoperative analgesia. All patients received a standard general anaesthetic which consisted of a rapid sequence induction with thiopentone 5–7 $mg\ kg^{-1}$ and suxamethonium 1 $mg\ kg^{-1}$. The trachea was intubated and the patient's lungs ventilated with 67% nitrous oxide and 0.5–2% isoflurane in oxygen as indicated clinically. Neuromuscular paralysis was maintained with vecuronium 0.1 $mg\ kg^{-1}$. Morphine 0.1 $mg\ kg^{-1}$ was given during operation. At the end of surgery, residual neuromuscular block was antagonized with neostigmine and glycopyrronium in appropriate doses. In the recovery area, patients were made comfortable by administration of increments of morphine 50 $\mu g\ kg^{-1}$ if required.

Before patients left the recovery area, the PCA machine (Graseby PCAS or 3300) was connected. The solution used consisted of morphine sulphate 1 $mg\ kg^{-1}$ diluted to 50 ml with 0.9% saline to give a concentration of 20 $\mu g\ kg^{-1}\ ml^{-1}$. The PCA machine was attached to the side arm of a Cardiff one-way valve incorporated into the i.v. infusion cannula. The settings used were a bolus dose of 1 ml (20 $\mu g\ kg^{-1}$) with a lockout interval of 5 min. Patients were allocated randomly (by means of a computer-generated list) to receive either this PCA regimen or the same PCA regimen with a background infusion of morphine 1 $ml\ h^{-1}$ (20 $\mu g\ kg^{-1}\ h^{-1}$).

After operation, patients breathed air and a monitoring regimen described previously [10] was used: Sp_{O_2}, ventilatory frequency, sedation score, pain score and nausea score, the number of demands

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made and the volume of solution infused were recorded hourly. Patients were visited three times daily by one of the authors, when the correct use of the trigger was emphasized and syringes were replaced if necessary. A named anaesthetist was available to deal with any problems relating to the PCA regimens. The PCA was discontinued when there was a consistent decline in use and patients were able to take oral analgesics.

Pain was scored using a four-point self-reporting score which has been validated previously [11]: A = asleep; 0 = no pain; 1 = not really sore; 2 = quite sore; 3 = very sore. Children were not awakened for assessment unless the nurse suspected oversedation; "A" was recorded on the chart at these times.

Sedation was scored using a four-point scale: 0 = eyes open spontaneously; 1 = eyes open to speech; 2 = eyes open when shaken; 3 = unrousable.

Nausea was scored on a four-point scale: 0 = none; 1 = nausea only; 2 = vomited once in the past 1 h; 3 = vomited more than once in the past 1 h.

If there was a pain score of 3, a sedation score of 3 or a nausea sore of 3, the named anaesthetist was asked to see the patient.

Results were analysed using the Mann–Whitney *U* test and chi-square tests as appropriate.

RESULTS

Details of the patients are shown in table I.

The total morphine consumption in the PCA+background group was significantly ($P < 0.01$) greater than that in the PCA only group. There was no significant difference in the amounts of morphine self-administered in the two groups.

TABLE I. *Patient characteristics and details of morphine usage (number, mean (range or* SD*)).* * *P < 0.05 between groups*

	PCA only		PCA+ background
Sex (M:F)	11:9		12:8
Age (yr)	9.6 (6–12)		10.2 (6–12)
Weight (kg)	33.5 (12.6)		32.8 (9.3)
Time of operation			
06:00–22:00	11		13
22:00–06:00	9		7
Duration of PCA (h)	36.9 (11.1)		37.1 (7.4)
Morphine usage			
($\mu g\ kg^{-1}$)	980 (434)	*	1635 (748)
($\mu g\ kg^{-1}\ h^{-1}$)	27.6 (12.7)	*	43.3 (14.8)
Background infusion			
($\mu g\ kg^{-1}$)			694 (189)
PCA ($\mu g\ kg^{-1}$)	980 (434)		941 (718)

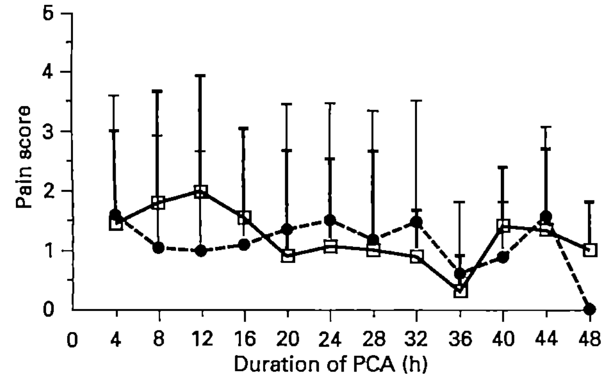

FIG. 1. Mean (SD) 4-hourly total pain scores in patients receiving PCA only (□) or PCA+background infusion (●).

For each patient, the hourly pain scores during each 4-h period were summed at 4-h intervals after the start of treatment and the means for patients in the two groups calculated (fig. 1).

There were no significant differences between the scores of the two groups in any of these periods.

There were significantly more instances of Sp_{O_2} less than 94% in the PCA+background group (143) than in the PCA only group (94) ($P < 0.001$). The smallest values of Sp_{O_2} recorded at any time (including those noted between hourly recordings) in the two groups were in the ranges 83–95% (mean 91%) in the PCA+background group and 88–94% (mean 92%) in the PCA only group.

Four occasions when ventilatory frequency was < 10 b.p.m. were noted in the same patient who was receiving a background infusion. Sp_{O_2} values at these times were 96%, 93%, 97% and 90%, respectively. The slowest ventilatory frequencies recorded in the two groups were 7–18 b.p.m. (mean 16 b.p.m.) in the PCA+background group and 12–20 b.p.m. (mean 17 b.p.m.) in the PCA only group.

The occurrence of sedation scores of 2 or greater were compared. There were no recordings of 3 in either group, but a significantly greater number of scores of 2 in the PCA+background infusion group (13) than in the PCA only group (4) ($P < 0.05$).

There was a significantly greater incidence of nausea and vomiting in the PCA+background group (37) than in the PCA only group (15) ($P < 0.01$). Antiemetics were given to one child in the PCA+background group.

The number of adverse events ($Sp_{O_2} < 94\%$, sedation scores $\geqslant 2$, nausea and vomiting) during the first 24 h of PCA use and subsequently did not differ between the groups.

The amount of time that patients in the two groups spent asleep was compared separately for the periods from 22:00 to 06:00 (night) and from 06:00 to 22:00 (day). Patients in the PCA+background group spent significantly ($P < 0.001$) more time asleep at night (198 h) than those in the PCA only group (154 h). There was no difference between the two groups in the time spent asleep during the day. Similar numbers of patients in both groups were operated on during the day and at night. The effect of the timing of operation on sleep pattern should, therefore, have been the same in both groups.

The analgesia provided in both groups was generally very good, with only 119 scores of 2 = quite sore or 3 = very sore from a total of 1521 scores (59 of 759 scores in the PCA only group and 60 of 762 in the PCA+background infusion group).

One child in the PCA+background group had the background infusion discontinued because of persistently decreased Sp_{O_2} when asleep, although the ventilation frequency was always 14 b.p.m. or greater.

DISCUSSION

Since its first use in children in 1987, PCA has become a widely used and effective treatment for acute pain in selected children as young as 5 yr. Most reports of its use in children are, however, simply descriptive and there are few controlled studies which compare different regimens in terms of efficacy, dosage and adverse effects.

The use of a concurrent background infusion with PCA in adults is currently an area of debate in the literature. It has been shown to improve pain relief in two studies [12, 13]. In one of these [12], the use of a background infusion after abdominal hysterectomy not only improved analgesia but was associated with improved sleep patterns and increased patient satisfaction without an increase in opioid-induced side effects. The other study [13] found that the use of a background infusion improved analgesia but was associated with an increase in opioid-related side effects such as nausea and vomiting. Significant respiratory depression was not observed.

Other studies have shown no benefit when a background infusion was added to the PCA regimen [14–16]. In these patients, morphine consumption was increased with no improvement in analgesia. The incidence of side effects was not increased and respiratory depression was not noted in the group receiving a background infusion.

In paediatric practice, one study [17] has compared PCA with and without a background infusion (in a comparison with i.m. injections). In that study, the infusion used was morphine $15\ \mu g\ kg^{-1}\ h^{-1}$. The PCA only group received bolus doses of $25\ \mu g\ kg^{-1}$ and the PCA+background infusion group received bolus doses of morphine $18\ \mu g\ kg^{-1}$. In both groups, lockout time was 10 min. There were no differences in morphine consumption, sedation, nausea or vomiting between the groups. Respiratory depression was not noted in any patient. The PCA+background group was found to have smaller pain scores than the PCA only group. This study used patient and nursing visual analogue scores for pain assessment, whereas our study used a patient self-report scale; this may account for the different findings of the two studies. Another study [18] in children found that PCA+background infusion did not improve analgesia, but was associated with a better sleep pattern than PCA alone, with no increase in the incidence of side effects.

Our study has found that the use of a background infusion of morphine $20\ \mu g\ kg^{-1}\ h^{-1}$ in a PCA regimen for children undergoing lower abdominal surgery produced a significant increase in morphine consumption without improving pain relief, and a significant increase in the incidence of side effects (respiratory depression, over-sedation and nausea or vomiting). Patients in the PCA+background group spent more time asleep at night than those in the PCA only group. There was no suggestion that the incidence of side effects increased with the duration of PCA use as the severity of postoperative pain declined.

The great variability in the morphine requirements of our patients, who had all undergone the same operation, is shown by the large standard deviation in the amount of morphine self-administered. The use of a fixed dose of morphine to cope with this wide variability would be expected to be unsuccessful. This may be why the use of a relatively small fixed infusion in addition to the PCA produced no discernible improvement in analgesia.

This is the first study to have shown an increased incidence of respiratory depression in patients receiving a background infusion compared with those receiving PCA only. Respiratory depression has been considered to be one risk associated with the addition of an infusion to PCA, but has not previously been shown to occur. The reason for this is probably that the previous studies comparing PCA with and without a background infusion [12–17] and the descriptive publications of patients receiving PCA+background have relied on intermittent timing of ventilatory frequency as an indicator of respiratory depression. This has been shown to be a late and insensitive monitor of respiratory depression [19, 20]. Arterial oxygen saturation (Sa_{O_2}) while breathing air is a more sensitive monitor of adequate ventilation and it has been suggested that pulse oximetry should be routine for the monitoring of children receiving PCA [21]. An Sa_{O_2} of 94% corresponds to a Pa_{O_2} of 10 kPa in healthy patients and indicates mild hypoxia and reduced reserve should further respiratory depression occur.

The use of PCA in adults also is associated with an incidence of respiratory depression. This may occur in up to 40% of patients breathing air after upper abdominal surgery [22]. Patients using PCA after lower abdominal surgery have been shown to be more likely to suffer episodes of mild hypoxaemia than patients receiving i.m. or extradural morphine [23]. Other studies have shown no difference between the incidences of hypoxaemia in adults receiving PCA and those receiving i.m. morphine [22].

In our study, 15% of Sp_{O_2} values were less than 94% in the PCA only group. The significance of this is unclear as there is no information on the incidence of hypoxaemia detected by pulse oximetry in children breathing air and given i.m. opioids.

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EFFECT OF ALCOHOL ON GASTRIC EMPTYING IN VOLUNTEERS†

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SUMMARY

We have examined the effect of alcohol on the gastric emptying rate of a liquid meal in 10 volunteers. Each volunteer was allocated randomly to receive, on three occasions, no alcohol, 3 units or 6 units of alcohol. Gastric emptying was measured using applied potential tomography. The rate of gastric emptying as measured by the time to 50% emptying (T_{50}) was delayed significantly ($P < 0.01$*) after alcohol 6 units (median 45.0 min (range 19–90 min)) compared with control (23.0 min (13–36 min)) and there was little change after alcohol 3 units (25.5 min (10–41 min)).* (Br. J. Anaesth. 1993; **71**: 674–676)

KEY WORDS

Gastrointestinal tract: alcohol. Measurement techniques: applied potential tomography, gastric emptying.

Regurgitation of gastric contents is of particular concern during anaesthesia for emergency surgery. Delayed gastric emptying in the perioperative period increases the likelihood of regurgitation and subsequent pulmonary aspiration of gastric contents [1]. Patients presenting for emergency surgery often give a history of recent alcohol intake. The reported effects of alcohol on human gastric emptying are inconsistenct—acceleration [2], delay [3, 4] or no effect [5] on gastric emptying after ingestion of alcohol all have been reported in the literature.

The purpose of this study was to assess the influence of alcohol on gastric emptying of a liquid meal using applied potential tomography.

SUBJECTS AND METHODS

Applied potential tomography

Applied potential tomography (APT) generates tomographic images of the resistivity of gastric contents using skin electrodes placed around the abdomen [6]. After ingestion of a test meal, changes in resistivity are measured and a profile of gastric emptying is generated. Sixteen electrodes are placed around the trunk at the level of the eighth costal cartilage; this level corresponds with the gastric fundus or body [7]. The electrodes are connected to a data collecting system which applies and records electrical potentials. An alternating current of 1 mA at 50 kHz is applied sequentially through adjacent pairs of electrodes. Measurements are made before and at 1-min intervals after the test meal. Data are stored on a disc by a Nimbus RM computer. The computer quantifies the image representing the stomach, and changes in resistivity with time within this area are recorded. When measuring gastric emptying using APT, it is necessary to use histamine type 2 receptor blockers to inhibit gastric acid secretion, as acid interferes with resistivity measurements [8]. Cimetidine does not affect the rate of gastric emptying [9] and was used in this study.

Study design

The study was approved by the local Ethics Committee and written informed consent was obtained from each subject. We studied 10 healthy, non-smoking male volunteers on three occasions at least 1 week apart in a randomized fashion, each acting as his own control.

After an overnight fast, cimetidine 800 mg was administered orally with water 50 ml. One hour later, the subject was allocated randomly to receive either no alcohol, 3 units (whisky 75 ml and water 25 ml) or 6 units (whisky 150 ml and water 50 ml) of alcohol (Famous Grouse Whisky). The alcohol was ingested over 20 min; 40 min later, with the subject sitting in a semisupine position at 45°, a liquid meal of beef consommé soup (Campbell's) 500 ml was given (energy content 87 kJ (21 kCal), protein 4.2 g, carbohydrate 1.2 g, osmolality 375 mosmol kg^{-1}). The change in resistivity with time within the stomach was recorded for 90 min and the time to 50% emptying (T_{50}) was recorded. A venous blood sample was obtained at the beginning of resistivity recordings, for measurement of ethanol concentration. The blood samples were assayed for alcohol within 24 h, by gas–liquid chromatography.

Statistical analysis

Data were analysed by Friedman's analysis of variance followed by Wilcoxon rank sum tests for paired data. $P < 0.05$ was taken as significant.

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†Provisional data from this study were presented to the Anaesthetic Research Society at Cambridge (*British Journal of Anaesthesia* 1992; **68**: 447P).

TABLE I. *Individual times and the median (range) time to 50% emptying (T_{50}) after no alcohol, 3 units and 6 units of alcohol.* *P < *0.05 compared with 6 units;* **P < *0.01 compared with control*

Subject No.	Time (min)		
	Control	3 units	6 units
1	27	41	27
2	22	27	50
3	23	24	63
4	36	16	45
5	24	65	90
6	27	49	45
7	13	10	19
8	17	24	36
9	29	42	90
10	23	11	26
Median	23.0	25.5*	45.0**
Range	13–36	10–41	19–90

RESULTS

All 10 volunteers completed the study. The mean age of the subjects was 31 yr (range 27–42 yr) and their weights 74.6 (SD 8.6) kg.

The individual and median (range) times to 50% emptying after no alcohol, 3 units or 6 units of whisky are shown in table I. Time to 50% emptying was significantly longer ($P < 0.01$) after 6 units of whisky compared with control; gastric emptying time also was increased (by 96%) after 6 units of whisky. There was little change after 3 units of whisky compared with control, but there was a significant difference in gastric emptying time after 3 units and 6 units of alcohol ($P < 0.03$).

The median (range) plasma ethanol concentrations after 3 units and 6 units were 31.5 (24–44) mg% and 85.5 (64–102) mg%, respectively.

DISCUSSION

This study has shown that 6 units of alcohol delayed gastric emptying of a liquid meal significantly compared with control, but 3 units of alcohol had little effect on gastric emptying.

Earlier studies produced conflicting results on the effects of alcohol on gastric emptying. The results of animal studies indicate consistently that administration of alcohol delays gastric emptying [10–12]. Data from human studies are less clear [2–5]. There are many differences in the design of these studies, such as the amount and type of alcohol-containing beverages, type of meal ingested, timing of the administration of alcohol relative to the meal and measurement of gastric emptying, and the method of measuring gastric emptying.

Some studies have shown enhancement of gastric emptying. Using the dye dilution method, Kaufman and Kaye [2] demonstrated acceleration of gastric emptying after 40 and 80 ml of ethanol compared with a glucose meal of similar osmolality and pH. The osmolality of the three meals was adjusted to be equal by the addition of glucose and sodium chloride. However, hypertonic glucose and sodium chloride are potent inhibitors of gastric emptying [4]. Therefore, the relative enhancement of gastric emptying by ethanol in this report was most probably the result of the retarding effect of hyperosmolar sodium chloride and glucose added to the control liquid meal.

Using the radioisotope method, Moore and colleagues [5] showed no significant delay in gastric emptying of solid and liquid meal after wine compared with control. The mean plasma ethanol concentration in their study (38.4 mg%) was similar to that achieved in the present study after 3 units of whisky (32.5 mg%), and in both studies gastric emptying was not significantly delayed. This suggests a dose-related delay in gastric emptying. Moore and colleagues gave the alcohol and the meal 10 min before measuring gastric emptying. We chose to give the alcohol 1 h before the meal and before measuring gastric emptying, in order to give the alcohol time to take effect.

In contrast, our data are consistent with those of other workers [3, 4]. A delay in gastric emptying of a solid meal after administration of 100% ethanol via a nasogastric tube was demonstrated using a scintigraphic technique [4]. A smaller concentration of ethanol was used in our study because ethanol is seldom drunk as a 100% solution. Barboriak and Mead [3] demonstrated a delay in gastric emptying of a solid meal after whisky 120 ml, using the scintigraphic method. However, rate of gastric emptying of the control meal was prolonged compared with that in our study (T_{50} of 105 min) and may have been caused by the high fat content (60 g) of the meal administered.

The mechanism of delay in gastric emptying caused by ethanol cannot be deduced from this study. Alcohol enhances postprandial release of gastrin [4], which may explain the delay [13]. Ethanol is known to delay the release of several neurotransmitters, including acetylcholine [14], which plays an important role in the regulation of gastric emptying. Ethanol has been shown also to decrease the contraction of gastric and small intestinal muscle [15]. The possible role of the congeners present in the whisky is not clear. However, the observation from previous work [4] that pure alcohol delays gastric emptying and that congeners are present in the small proportion of 0.003–0.4% [16] suggest that they are of minor importance.

In conclusion, we have shown that 6 units of whisky delayed gastric emptying of a liquid meal significantly compared with control and 3 units appeared to have little effect. These data suggest that a patient with a history of recent alcohol intake is likely to have delayed gastric emptying and is therefore at greater risk of aspiration of gastric contents during anaesthesia. We therefore have positive evidence to suggest that anaesthesia should be delayed longer in patients who have recently ingested alcohol than in those who have not.

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TROPISETRON FOR POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS AFTER GYNAECOLOGICAL SURGERY

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SUMMARY

*In a double-blind study, we have compared the prophylactic antiemetic effect of tropisetron 5 mg (Navoban, a 5-HT_3 receptor antagonist) with that of placebo, both given as a short i.v. infusion approximately 15 min before wound closure in patients undergoing gynaecological surgery. Perioperative anaesthetic care was standardized and patients were observed for at least 24 h after operation. The 35 patients given tropisetron and 34 given placebo treatment were well matched for characteristics. Vomiting occurred in 26% of tropisetron-treated patients, compared with 59% of placebo-treated patients (*P = *0.006); 69% of tropisetron-treated patients suffered nausea, compared with 88% of placebo-treated patients (*P = *0.05). In addition, patients judged the antiemetic treatment with tropisetron as more effective than the placebo treatment (visual analogue score 71 vs 51 mm (*P = *0.003)).* (Br. J. Anaesth. 1993; **71**: 677–680)

KEY WORDS
Vomiting: nausea, tropisetron.

Postoperative nausea or vomiting occur frequently after surgery under general anaesthesia. Abdominal and gynaecological surgery are particularly associated with postoperative nausea or vomiting, the reported incidence ranging from 1 to 80%, with an estimated 20–40% average [1, 2]. In a pilot study to determine the overall incidence of nausea and vomiting in the recovery ward, including all patients ($n = 446$) undergoing all types of anaesthetic techniques and surgery, it became clear that the greatest incidence of vomiting and nausea occurred in the gynaecological patients under general anaesthesia [Langenberg and Zomers, unpublished data]. Furthermore, postoperative nausea or vomiting are the most frequent factors preventing patients returning home at the end of the day after day-case surgery [3] or necessitating readmission to hospital [4], and this emphasizes the need for an effective antiemetic [5].

Tropisetron, a selective 5-HT_3 receptor antagonist, proved effective against nausea and vomiting induced by chemotherapy when administered as an optimal once-daily dose of 5 mg [6]. The success of this and other 5-HT_3 receptor antagonists [7] in preventing chemotherapy-induced nausea and or vomiting, led to study of their efficacy in treating postoperative nausea and vomiting [8–10]. In this study we have compared the efficacy of tropisetron with that of placebo for the prevention of postoperative nausea and vomiting in patients undergoing a gynaecological operation under standardized anaesthetic conditions.

PATIENTS AND METHODS

After obtaining informed consent and approval from the local Ethics Committee, we studied 70 consecutive non-pregnant women aged 18–75 yr undergoing gynaecological surgery under general anaesthesia (tables I, II). Day-case patients, those with confounding co-existing medical conditions and those receiving concomitant medications that could

TABLE I. *Characteristics of the two treatment groups (mean (range), mean or No. (%)). *Wilcoxon test for age, weight and height; otherwise, chi-square test*

	Tropisetron	Placebo	*P**
No. patients entered	35	34	
Age (yr)	48 (27–73)	47 (28–73)	0.66
Weight (kg)	66	68	0.25
Height (cm)	165	167	0.11
No. of patients with co-existent diseases	13 (37)	10 (29)	0.51
Patients with concomitant medication	11 (31)	14 (41)	0.40
Patients with previous			
General anaesthesia	27 (77)	27 (82)	0.63
GA, with emesis	14 (52)	13 (48)	0.79

TABLE II. *Types of operation performed (No.)*

	Placebo ($n = 34$)	Tropisetron ($n = 35$)
Abdominal hysterectomy	15	12
Vaginal hysterectomy	7	11
Ovariectomy	1	1
Gynaecological laparotomy	2	4
Other	9	7

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TABLE III. *Doses of sufentanil and naloxone administered*

	Tropisetron ($n = 15$)	Placebo ($n = 18$)	P
Sufentanil (µg)	10–70	10–80	0.42
Naloxone (µg)	20–70	20–80	0.78

interfere with the evaluation of the study drug, in particular phenothiazines and prokinetic drugs, were excluded.

Antiemetic treatment was randomized in a double-blind, placebo-controlled study with two parallel groups. The study adhered to the conditions laid down in the Declaration of Helsinki and its amendments and was carried out in accordance with the "Guidelines of Good Clinical Practice".

Premedication was with diazepam 10 mg. Anaesthesia was induced with etomidate 0.2 mg kg^{-1}, atracurium 0.3 mg kg^{-1} and sufentanil 0.3 µg kg^{-1} and the trachea was intubated. After induction, a gastric tube was inserted to avoid gastric dilatation. Anaesthesia was maintained with 70 % nitrous oxide and isoflurane (preferred concentration 0.5 %) in 30 % oxygen, supplemented with atracurium and sufentanil as necessary (table III). At the end of the anaesthesia, residual neuromuscular block was antagonized with prostigmine 1 mg and atropine 0.5 mg i.v.; small doses of naloxone (20–40 µg) were given only if necessary. The nasogastric tube was removed in the operating room. For postoperative analgesia, paracetamol 500 mg 6-hourly and piritramide 20 mg as required were prescribed. Two patients in the ICS group and five patients in the placebo group received extradural 0.25 % bupivacaine at their own request. The extradural infusion of 0.25 % bupivacaine was commenced when the patient left the recovery room.

As antiemetic prophylaxis, patients received either placebo or tropisetron 5 mg given as a short infusion approximately 15 min before wound closure. A 5-mg dose of tropisetron was chosen because it had proved to be optimal for treatment of nausea and vomiting induced by various highly emetic chemotherapy regimens [6]. For rescue antiemetic treatment, the patient was given a suppository containing domperidone 60 mg. If nausea or vomiting persisted for more than 1 h thereafter, another domperidone suppository was given.

Information on postoperative nausea and vomiting over the 24-h period after administration of the study medication was obtained from three sources: nursing observation in the recovery room and on the ward; the attending anaesthetist interviewed the patient on the day after the operation and completed a checklist; the patient completed a VAS score for self-assessment of nausea and vomiting and well-being on the day after surgery (VAS score: 0 mm = severe complaints of nausea and vomiting—not satisfied; 100 mm = no complaints of nausea and vomiting—completely satisfied).

Patients underwent physical examination, blood tests and an ECG. The laboratory tests consisted of haemoglobin concentration, leucocytes and platelet counts and measurements of serum concentrations of electrolytes, creatinine and liver enzymes ALAT, ASAT and alkaline phosphatase. These tests were repeated at 24–48 h after the administration of the study drug. The operations were performed with standard anaesthetic monitoring, including arterial pressure, heart rate (ECG) and pulse oximetry. The attending anaesthetist recorded all adverse events, including any unusual symptoms which the patient mentioned during the interview on the day after the operation. The time between end of anaesthesia and opening the eyes was noted.

Statistical evaluation and end-points

We examined the hypothesis that at least 40 % of the patients in the placebo group would suffer from nausea and vomiting and that tropisetron would reduce the incidence of nausea and vomiting to approximately 10 %. A sample size of 38 patients per treatment group would provide 80 % power to detect a difference of treatment success of 60 % in the placebo group and 90 % in the tropisetron group at the $\alpha = 0.05$ significance level [10]. Grouped data were analysed by means of z tests or Wilcoxon tests and contingency tables by means of chi-square tests. Two-sided values of probability P were added as appropriate.

Primary efficacy end-points were the number of episodes of vomiting and nausea recorded by the nurses and the patients. Secondary efficacy end-points were the frequency of alternative antiemetic therapy and the subjective ratings of the patient VAS score. Tolerance and safety were assessed from the adverse event recordings and the anaesthesia records.

Data were analysed with "Biomedical Computer-programmes (BMPD) Statistical Software Manual" version 1988, on a Compac PC, Dos version 3.31.

RESULTS

We studied 70 patients; one patient given placebo was excluded because of missing data. The results are presented for 35 patients who received tropisetron and 34 who received placebo. The groups were comparable (table I). The most common co-existing diseases are shown in table IV for the two groups. Approximately 50 % of the patients in each group who previously underwent general anaesthesia had suffered nausea or vomiting on those occasions.

Anaesthesia and postoperative analgesic medications were comparable in the two groups.

TABLE IV. *Co-existing medical conditions*

	Placebo ($n = 10$)	Tropisetron ($n = 13$)
Hypertension	3	5
Diabetes mellitus	1	2
Ventricular extrasystole	0	2
Anaemia	0	2
Atrial fibrillation	2	0
Multiple sclerosis	1	0
Constipation	1	0
Spastic colon	0	1
Carotid artery insufficiency	1	0
Epilepsy	1	0

TABLE V. *Results of patient questionnaire.* † *Mean (SD) visual analogue score on scale from 0 (complaints about nausea or vomiting—maximum dissatisfaction) to 100 (no nausea and vomiting—maximum satisfaction).* **Chi-square test, except Wilcoxon test for overall satisfaction score*

	Tropisetron ($n = 35$)		Placebo ($n = 34$)		
	Yes	No	Yes	No	P*
Remember recovery (%)	77	23	76	24	0.95
If yes:					
Feel sick (%)	33	67	50	50	0.22
Vomited (%)	7	93	35	65	0.015
On the ward					
Feel sick (%)	57	43	85	15	0.01
Vomitted (%)	20	80	53	47	0.005 0.07
Rescue treatment (%)	43	57	64	36	0.25
Effect of rescue treatment (%)	65	35	45	55	
Overall satisfaction score (mm)†	71 (26)		51 (30)		0.003

Twenty-six percent of tropisetron-treated patients vomited during the 24-h observation period, compared with 59% of placebo-treated patients ($P = 0.006$). In the recovery room, only three (8%) tropisetron-treated patients vomited, compared with 10 (29%) placebo-treated patients ($P < 0.001$). On the ward, eight (23%) tropisetron-treated patients vomited, compared with 19 (56%) placebo-treated patients ($P < 0.001$). Sixty-nine percent of tropisetron-treated patients experienced nausea, compared with 88% of placebo-treated patients ($P = 0.05$). When the patients with postoperative extradural analgesia were excluded, the frequencies of nausea and vomiting were unchanged.

The time between discontinuing nitrous oxide and the patient opening the eyes was 3.6 (SD 3.2) min in the tropisetron group and 3.4 (2.4) min in the placebo group ($P = 0.87$).

Overall, patients in the tropisetron group were significantly more satisfied with their treatment than those in the placebo group. The overall satisfaction score correlated well with the frequency of vomiting ($r = -0.64$; $P < 0.001$) and the frequency of episodes of nausea ($r = -0.55$; $P < 0.001$) (table V).

There were no changes in biochemical tests after operation compared with before operation. Postoperative changes in haemoglobin concentration and PCV could be explained on the basis of blood loss and haemodilution.

DISCUSSION

The incidence of vomiting and especially that of nausea in our placebo group were greater than those reported previously [1, 2, 5, 7–9]. The choice of patient and period of observation on the ward may explain this finding. Women are known to experience a greater incidence of postoperative nausea and or vomiting than men. Gynaecological operations particularly predispose to postoperative nausea and vomiting. In addition, the interaction between the patients, nursing staff and anaesthetist for data collection may have influenced the high incidence of nausea reported in this study. However, the data were consistent between the two groups and we believe that the extent of postoperative nausea has been underestimated in the past.

Tropisetron, in common with ondansetron [7, 8], controlled vomiting more effectively than nausea. This finding corresponds with data for tropisetron used to treat chemotherapy-induced nausea and vomiting [6]. However, the pathogenesis of nausea may differ from that of vomiting; for example, severe pain and anxiety may have contributed to nausea, but not to vomiting. It is not likely, therefore, that one drug will be equally effective in treating both nausea and vomiting.

There were no differences between the groups in the time between the end of operation and opening the eyes on request or the duration of stay in the recovery room. Tropisetron did not prevent nausea and vomiting in all patients and, in retrospect, the timing of its administration may be judged not to have been ideal. Shortly before wound closure, most of the anaesthetic medication had been given and this may already have liberated the serotonin that activates the receptors implicated in nausea and vomiting reflexes. At the time of planning the study, however, we did not know if tropisetron would interfere with haemodynamic stability during induction and crucial events during the operation.

The possibility that the antiemetic medication may have interfered with anaesthetic care was examined by comparing the vital signs, recovery times, the incidence of postoperative amnesia and the analgesic requirements during and after operation. However, there were no significant differences between the two groups in these variables. Also, tropisetron did not affect laboratory variables or the ECG, and no side effects were detected. We conclude that the prophylatic administration of tropisetron 5 mg before the end of the operation effectively reduced the incidence of postoperative nausea and vomiting, without any ill effects.

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EFFECT OF TROPISETRON, A 5-HT_3 RECEPTOR ANTAGONIST, ON ANALGESIA AND NAUSEA AFTER INTRATHECAL MORPHINE

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SUMMARY

We have studied the effect of tropisetron, a 5-HT_3-receptor antagonist, on postoperative nausea, vomiting and pain in 54 patients, aged 50–83 yr, after major hip or knee surgery. The patients were given subarachnoid injection of plain 0.5% bupivacaine, mixed with preservative-free morphine 0.3 mg, for surgical and postoperative analgesia. In a double-blind fashion, either tropisetron 5 mg (1 mg ml^{-1}) or saline 5 ml was injected i.v. 30 min after spinal administration of bupivacaine and morphine. The number of patients needing i.m. oxycodone for pain relief, the total number of oxycodone doses or the mean time to the first i.m. oxycodone administration did not differ significantly between the two groups. The number of patients who became nauseated or vomited during the observation period did not differ significantly between groups. Seventeen patients had nausea and 11 vomited in the tropisetron group, compared with 20 and 13, respectively, in the control group during the first 24 h. (Br. J. Anaesth. 1993; **71**: 681–684)

KEY WORDS

Anaesthetic techniques: spinal. Anaesthetics, local: bupivacaine. Analgesics: morphine, oxycodone. Vomiting: tropisetron.

Intrathecal morphine provides good pain relief after orthopaedic surgery of the lower extremities [1–3]. Unfortunately, the use of spinal morphine, even in small doses, is often associated with unpleasant side effects such as urinary retention, pruritus and nausea and vomiting [4]. Specific 5-HT_3 receptor antagonists are beneficial in attenuating nausea and vomiting induced by chemotherapeutic agents in cancer patients [5–7]. Recently, two 5-HT_3 antagonists, ondansetron [8–10] and tropisetron [11] have been introduced for the prevention and treatment of emesis after general anaesthesia.

It is important to consider that 5-HT receptor antagonists may influence pain perception in addition to nausea and vomiting. In the spinal cord, 5-HT is involved in antinociception mechanisms [12, 13]. 5-HT increases nociceptive thresholds and tropisetron has been shown to antagonize 5-HT-induced antinociception, suggesting an important role for 5-HT_3 receptors in modulating spinal nociceptive responses [14]. On the other hand, 5-HT_3 receptor antagonists, including tropisetron, have been found to reduce certain types of pain (chemical and inflammatory) by peripheral 5-HT_3 receptor mechanisms [15, 16].

The efficacy of 5-HT_3 antagonists for prevention of nausea and vomiting after intrathecal administration of morphine has not been investigated. The present study was designed to see if a prophylactic 5-mg dose of i.v. tropisetron influences the incidence of nausea and vomiting, and the quality of postoperative analgesia in patients undergoing hip or knee operations (arthroplasty or osteotomy) under bupivacaine–morphine spinal anaesthesia.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of Surgical Hospital/Helsinki University Central Hospital, and the patients gave informed consent.

We studied 54 ASA I–III patients, undergoing major orthopaedic hip or knee surgery in this randomized, double-blind study (table I). All patients were premedicated with oral diazepam 5 mg (weight 60 kg or less), 10 mg (61–80 kg) or 15 mg (weight greater than 80 kg). Patients older than 75 yr were given diazepam 5 mg (80 kg or less) or 10 mg (> 80 kg). The subarachnoid puncture was per-

TABLE I. *Characteristics and perioperative data of the patients (numbers of patients, mean (range or SD) or median (range))*

	Tropisetron	Saline
Age (yr)	69.5 (52–86)	66.6 (49–85)
Height (cm)	164 (9.6)	166 (9.8)
Weight (kg)	79 (14.7)	75 (13.6)
Sex (F/M)	19/8	20/7
Type of surgery (hip/knee)	12/15	13/14
Analgesia level at 60 min	T4 (T11–C8)	T6 (T12–C8)
Methylmetacrylate cement used	22	21
Blood loss during operation and in postanaesthesia care unit (ml)	920 (805)	1200 (977)
Need for benzodiazepines during operation	6	9
Need for fentanyl during operation	4	5

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formed in the midline of the L3–4 interspace (25- or 27-gauge needle), with the patient in the lateral position. Preservative-free morphine 0.3 mg was mixed with plain 0.5 % bupivacaine 20 mg (a 15-mg dose was used in two patients in the tropisetron and one patient in the saline group) before injection. The level of analgesia to pinprick 60 min after the injection was recorded.

Within 30 min after subarachnoid injection of bupivacaine with morphine, one of the investigators injected either tropisetron 5 mg (3α-tropanyl-1H-indole-3-carboxylic acid ester; Sandoz Ltd, Basel, Switzerland) or an equivalent volume of saline i.v. over 2–3 min using a coded syringe. The syringe was filled with the test solution by a trained nurse, according to a note in a sealed envelope. The investigators were unaware of the agent injected.

Non-invasive arterial pressure (oscillotonometry), ECG, heart rate and Sp_{O_2} were monitored in the operating room and in the postanaesthesia care unit. I.v. fluids (Ringer's acetate, hydroxyethyl starch) and erythrocyte concentrate transfusions were given on an individual basis, according to our clinical routines. Oxygen 2–3 litre min^{-1} was delivered via a nasal catheter during surgery. During operation, fentanyl 50 µg i.v. for analgesia and diazepam 2.5–5 mg i.v. for sedation were administered, if required. Pain and the need for medication were assessed on an arbitrary scale: 0 = no pain; 1 = mild pain (opioids not needed); 2 = pain (opioids needed); 3 = severe pain (opioids needed immediately) after operation, for 24 h. Ketoprofen 100 mg orally for mild pain (score 1) or oxycodone 0.1–0.14 mg kg^{-1} i.m. for more severe pain was given on request. The patients were confined to bed for 24 h. On the ward, they were allowed to drink and eat light meals.

The occurrence of nausea and vomiting was recorded continuously during the patient's stay in the postanaesthesia care unit and on the ward. Pruritus and micturition problems (need for bladder catheterization) and other observations were noted. Patients were assessed for pain, sedation and headache at 6-h intervals: at 15:00 on the ward (by investigator), at 21:00 (by a trained nurse), at 03:00 (by a trained nurse) and at 09:00 (by investigator) and once more if the 24-h observation period was incomplete at 09:00. For analyses, analgesia requirement and episodes of nausea or vomiting were grouped at 6-h intervals. In the case of persistent vomiting, droperidol 1.25 mg i.m. was given. In the recovery room, metoclopramide 10–20 mg i.v. was given.

Statistical analysis

Sample size was established using a sample size calculation to compare the prevalence of nausea in these patients. For this analysis, we used the prevalence published from similar groups of subjects [17–19] and set critical error levels at $\beta = 0.25$ and $\alpha = 0.05$.

Statistical significance between the mean values was evaluated using Student's t test and between frequencies using Fisher's exact test. The Mann–Whitney U test was used for level of spinal analgesia.

RESULTS

The characteristics of the patients and perioperative data in the two groups were comparable (table I).

Two patients in the saline group and three in the tropisetron group were given ketoprofen. The patients in the tropisetron group and one in the saline group who were given ketoprofen also needed oxycodone (table II). There were no differences between the groups in the number of patients requiring supplementary oxycodone, the total number of doses or the time from the injection of intrathecal morphine to the first administration of i.m. oxycodone. The number of patients who were completely pain-free (score 0) decreased over time at a similar rate in both groups (table III).

There was no statistically significant difference between the number of patients in the two groups who became nauseated or vomited during the observation period (table IV). In the tropisetron group, there were 11 patients who had no nausea and seven who had nausea on only one occasion; the respective numbers of patients in the saline group were six and 11 (ns). The total number of episodes of nausea, or vomiting, or both, occurring during 7–18 h from the injection of the test drug was greater in the saline group (fig. 1) (ns). Two patients in the tropisetron and one patient in the saline group needed metoclopramide, and eight patients in the tropisetron and six in the saline group required droperidol.

TABLE II. *Postoperative requirement for oxycodone and mean* (SD) *time to first dose. No significant difference between groups*

	No. patients	No. doses	Time to first dose (h)
Tropisetron	23	53	11.8 (5.9)
Saline	20	44	13.1 (6.0)

TABLE III. *Pain scores (no significant differences between groups)*

	Number of patients				
	Post-anaesthesia care unit	15:00	21:00	3:00	9:00
Tropisetron					
Score 0	26	24	17	17	14
Score 1	1	3	6	6	10
Score 2	0	0	3	4	1
Score 3	0	0	1	0	2
Saline					
Score 0	26	22	18	19	13
Score 1	1	4	7	5	8
Score 2	0	1	1	2	4
Score 3	0	0	1	1	2

TABLE IV. *Number of patients experiencing nausea/vomiting, urinary retention requiring catheterization or pruritus. No significant difference between groups*

	Nausea/vomiting	Urinary retention	Pruritus
Tropisetron	17/11	10	8
Saline	20/13	13	12

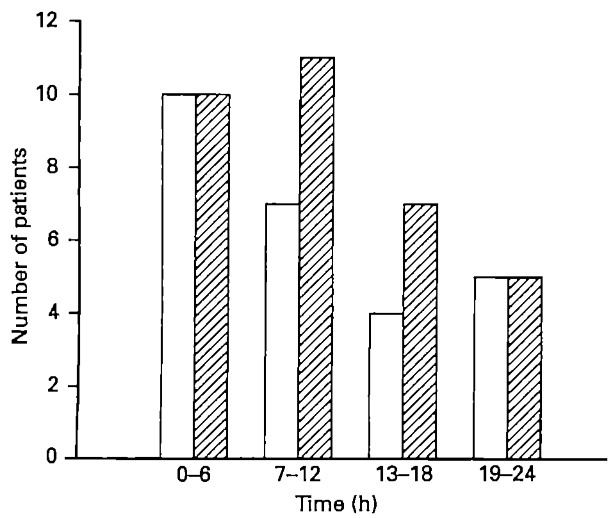

FIG. 1. Incidence of nausea in the tropisetron (□) and saline (■) groups. No significant difference between groups.

Pruritus and urinary retention occurred in almost the same number of patients in the two groups (table IV). No postdural puncture headache or ventilatory frequencies less than 10 b.p.m. were observed.

DISCUSSION

Our data indicate that prophylactic i.v. tropisetron had no observable influence on intrathecal morphine analgesia after major hip and knee surgery. Only a small, non-significant reduction in the number of episodes of nausea could be detected after operation for 7–18 h (fig. 1). The timing and dose of the tropisetron administration were based on experience in the prevention of chemotherapy-induced emesis [5] and the relatively long elimination half-life (approximately 8 h) of the drug in man (production information, Sandoz Ltd, Basel, Switzerland). Tropisetron was administered 30 min after intrathecal morphine. However, this may be considered as prophylactic, since intrathecally administered morphine reaches the respiratory centre (which is close to the chemoreceptor trigger zone and vomiting centre) by 60 min [4].

The incidence of nausea in the present study (59 % and 74 %) was greater than in two of our recent studies in orthopaedic patients: when bupivacaine spinal anaesthesia without addition of intrathecal morphine was given, the postoperative incidence of nausea was 37.5 % [17] and when morphine 0.1 mg 24 h^{-1} was added, the incidence was 45 % [18]. In a recent study, after intrathecal morphine 0.2 mg, the incidence of nausea was 61 % [19]. Although the causes of postoperative nausea after major orthopaedic surgery are multifactorial (opioids, surgery, transfusions, methylmetacrylate, etc.) it is obvious that the disturbingly high incidence of nausea and vomiting in the present study was caused largely by intrathecally administered morphine.

Probably the most important mechanism by which morphine induces nausea is a direct action on dopamine receptors of the chemoreceptor trigger zone [20] in the area postrema. Emesis-inducing gastrointestinal effects of morphine include decrease in gastric motility and spasms and non-propulsive contractions of the upper part of the small intestine [21]. There is also a vestibular component in morphine-induced nausea, which may not have played any major role in the present study, as the patients were recumbent in bed for the entire 24-h period. Considering the relatively small dose of intrathecal morphine used (0.3 mg), the blood concentrations of morphine were probably too small to exert systemic effects. Therefore, it may be assumed that morphine migrated slowly to the chemoreceptor trigger zone and provoked nausea by acting directly via stimulation of the zone [22]. Intrathecally distributed morphine may diffuse directly through the ependymal floor of the fourth ventricle, thereby reaching the area postrema. This part of the central nervous system is known to contain large numbers of 5-HT_3 receptors [23, 24].

It has been suggested that another 5-HT_3 receptor antagonist, ondansetron, may be a useful antiemetic in surgical patients after general anaesthesia [9, 10]. These studies, in addition to experiences from the use of this drug in chemotherapy-induced nausea and vomiting [25], indicate that the 5-HT_3 antagonist is perhaps more effective in reducing vomiting than in preventing nausea. In contrast, we could not demonstrate such a differential action by a single prophylactic dose of tropisetron.

Side effects such as headache and sedation, which occur in cancer patients during tropisetron treatment [5], were not observed in our patients.

The lack of significant effect of tropisetron on nausea and vomiting after subarachnoid morphine in the present study is not suggestive of an important role of 5-HT_3 receptor involvement in this particular type of nausea. The nausea associated with cisplatin therapy is at least in part caused by the release of 5-HT from the viscera and activation of 5-HT_3 receptors [7] and it can therefore be attenuated to a clinically significant degree with specific 5-HT_3 antagonists. There are also suggestions that the 5-HT_3 receptor antagonists may act on peripheral receptors found in abdominal visceral afferent neurones [26], which could explain the poor antiemetic effect of the 5-HT_3 antagonist in the present subarachnoid morphine study. Metoclopramide, one of the rescue antiemetics used in our study, might be better suited for the prevention and treatment of nausea induced by subarachnoid morphine [27]. Metoclopramide increases lower oesophageal sphincter tone and enhances gastric and bowel motility and has antidopaminergic [28] and, in large doses, also an anti-5HT receptor action [29].

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DOUBLE-BLIND COMPARISON BETWEEN DOXAPRAM AND PETHIDINE IN THE TREATMENT OF POSTANAESTHETIC SHIVERING

P. SINGH, V. DIMITRIOU, R. P. MAHAJAN AND A. W. A. CROSSLEY

SUMMARY

Sixty patients who shivered after routine surgery under general anaesthesia were allocated randomly to receive normal saline ($n = 20$), doxapram 1.5 mg kg^{-1} ($n = 20$) or pethidine 0.33 mg kg^{-1} ($n = 20$). Both doxapram and pethidine were effective in treating postoperative shivering 2–3 min after i.v. administration. In the group who received normal saline, 15 patients were still shivering 10 min after treatment, whilst in the doxapram group only three patients were shivering at that time. In the pethidine group, all patients had stopped shivering by 7 min after treatment. We conclude that both doxapram and pethidine were effective in the treatment of postoperative shivering. (Br. J. Anaesth. 1993; **71**: 685–688)

KEY WORDS

Complications: shivering. Analeptics: doxapram. Analgesics: pethidine.

Postanaesthetic shivering is a common phenomenon with a reported incidence varying from 5 to 65% [1–8]. It is important to prevent or treat postoperative shivering because of the distress it causes and the consequences involved, which may include an increase in metabolic rate of up to 400%, arterial hypoxaemia, lactic acidosis, increased intraocular pressure and difficulty in monitoring [5, 6, 9–11]. It has been shown that suppression of shivering decreases oxygen consumption and improves haemodynamic stability in the postoperative period [12].

Among the pharmacological methods of treating shivering, pethidine has been shown consistently to be effective [12–14]. Recently, Sarma and Fry found doxapram was effective [15], but there are no studies which compare doxapram with pethidine. In this study, we have compared the effectiveness of pethidine and doxapram in a placebo-controlled, double-blind manner.

PATIENTS AND METHODS

The study was approved by the local hospital Ethics Committee. We studied 60 patients (both genders), ASA I or II, who had undergone routine orthopaedic or otolaryngological surgery and developed shivering within 10 min of admission to the recovery room. As a consequence of the patients being selected as they were recovering from anaesthesia, their consent was not considered valid, and with the agreement of our Ethics Committee we did not obtain informed consent. Those patients with a history of hypertension, coronary artery disease, other cardiorespiratory or neuromuscular pathology were excluded.

Patients received the routine care undertaken for postoperative shivering in this hospital: they received oxygen by face mask and were covered by a heat-reflective blanket. In addition, each patient received an i.v. injection of doxapram 1.5 mg kg^{-1}, pethidine 0.33 mg kg^{-1} or normal saline from identical syringes according to the randomization. All syringes were prepared by recovery nursing staff following written instructions removed from a sealed envelope.

The investigator who gave the i.v. injection was unaware of the treatment received by the patient, and assessed the shivering grade (table I) before (time 0) and then at every subsequent 1 min after treatment for 10 min. To limit between-observer bias, the number of investigators assessing the shivering grade was restricted to two (P.S. and V.D.). Each assessed an equal number of patients from all three groups. Oxygen saturation, heart rate and arterial pressure were recorded before and every 1 min after treatment for 10 min. Axillary temperature was measured immediately before the treatment was administered. Surgical procedure, duration of anaesthesia and anaesthetic technique were recorded for each patient.

TABLE I. *Classification of shivering*

Grade	Clinical signs
0	No shivering.
1	One or more of: piloerection, peripheral vasoconstriction, peripheral cyanosis without other cause, but without visible muscular activity.
2	Visible muscular activity confined to one muscle group.
3	Visible muscular activity in more than one muscle group.
4	Gross muscular activity involving entire body.

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Statistical analysis was performed using ANOVA for evaluation of homogeneity of groups, by comparison of means between the different treatment groups with regard to age, weight, duration of anaesthesia, heart rate and arterial pressure. For comparison of gender, anaesthetic drugs, mode of ventilation and shivering between groups, chi-square test was used.

RESULTS

The three groups were comparable with regard to age, weight and gender (table II). There were no statistically significant differences in the duration of anaesthesia, mode of ventilation, use of volatile inhalation agents or the use of intraoperative opioids between the three groups (table III), and no statistically significant difference in axillary temperature or shivering grade between the groups at the time of entry into the study. The temperature range for patients in the saline group was 35.6–37.7 °C, in the doxapram group 35.2–37.0 °C and in the pethidine group 34.8–37.5 °C. There was a preponderance of shivering grades 3 and 4 in all groups.

The effect of treatment may be seen in figure 1 and table IV. There was a statistically significant difference between groups in incidence and severity of shivering: $\chi^2 = 9.40$, $P < 0.01$ and $\chi^2 = 16.65$, $P < 0.05$, respectively at 2 min after treatment and $\chi^2 = 19.8$, $P < 0.001$ and $\chi^2 = 34.77$, $P < 0.001$, respectively at 3 min after treatment, remaining so until the end of the study.

Fifteen patients (75%) in the saline group and three patients (15%) in the doxapram group were still shivering 10 min after treatment, whilst all patients stopped shivering at 7 min after treatment with pethidine. Throughout the study, more patients shivered in the doxapram group than in the pethidine group, although this was significant only at 3 min and 7 min after treatment ($\chi^2 = 5.23$ and 4.44 respectively, $P < 0.05$ at both times). No patient who was successfully treated subsequently returned to shivering during the study period.

TABLE II. *Patient characteristics in the three study groups (mean (range or SD) or absolute values)*

	Saline	Doxapram	Pethidine
Sex (M:F)	11:9	9:11	12:8
Age (yr)	29.6 (18–46)	31.5 (18–56)	34.2 (18–55)
Weight (kg)	69.7 (11.4)	69.1 (11.8)	76.5 (10.9)
Axillary temp. (°C)	36.2 (0.3)	36.1 (0.3)	36.2 (0.4)

TABLE III. *Anaesthetic data for the three groups (mean (range) or absolute numbers)*

	Saline	Doxapram	Pethidine
Operation time (min)	49.0 (25–90)	59.75 (25–130)	76.7 (20–240)
Volatile agent			
Halothane	13	15	16
Enflurane	7	4	3
Isoflurane	0	1	1
Opioid agent			
Morphine	10	13	11
Fentanyl	15	10	12
Alfentanil	2	1	2
IPPV	5	6	6

TABLE IV. *Distribution of patients (absolute numbers) according to shivering grade at the time of admission (time 0) and 2 and 3 min after treatment. S = Saline; D = doxapram; P = pethidine*

Shivering grade	Time 0			2 min			3 min		
	S	D	P	S	D	P	S	D	P
4	7	10	10	5	2	1	4	0	0
3	11	7	10	10	5	7	11	4	2
2	2	3	0	2	5	1	0	5	1
1	0	0	0	1	2	0	3	2	1
0	0	0	0	2	6	11	2	9	16

DISCUSSION

Our results indicate that both doxapram and pethidine were effective in treating postoperative shivering. Pethidine had a significantly better success

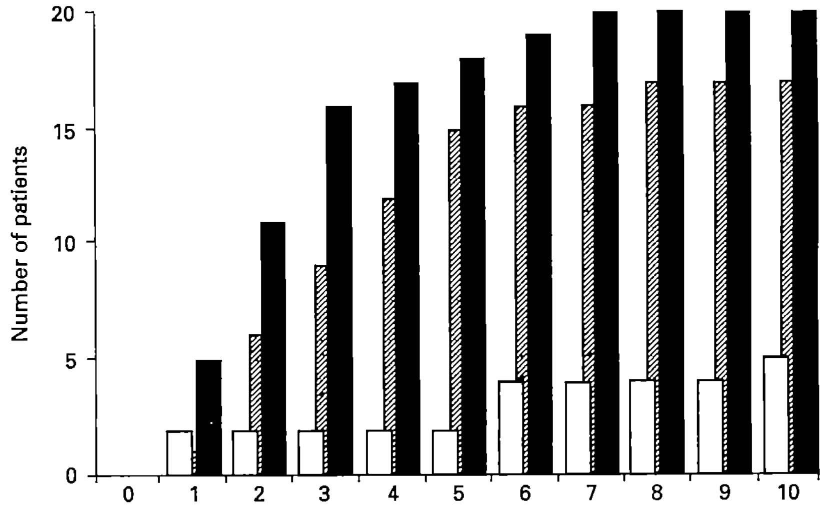

FIG. 1. Number of patients ceasing to shiver after treatment at each time interval. ■ = Pethidine; ▨ = doxapram; □ = saline. *n* = 20 in each group.

rate at 3 and 7 min after administration of treatment, with a success rate of 100 %, compared with 85 % for doxapram.

Shivering grade 1 was not an exclusion criterion, but there were no patients of shivering grade 1 entered into the study. Their absence may be explained by two possible mechanisms. It is possible that grade 1 represents a stage of recovery from postoperative shivering, so that patients who are stopping shivering after operation (either spontaneously or secondary to treatment) pass through this stage before they ultimately stop shivering. This view is supported by data from a previous study [8]. An alternative explanation may be that grade 1 is easy to miss unless it is specifically sought.

The aetiology of postanaesthetic shivering remains inadequately understood. This has led to various suggestions regarding the possible mechanisms and the mode of therapy. Amongst the suggested mechanisms are uninhibited spinal reflexes [4], pain [16], decreased sympathetic activity [17], adrenal suppression [7] and a normal thermoregulatory response to intraoperative heat loss [7, 18]. It has also been appreciated that shivering may not always be related to hypothermia in the postoperative period [19, 20].

A variety of drugs have been used to control postanaesthetic shivering, including methylphenidate [21], orphenadrine [22], magnesium sulphate [23], pancuronium [5] and various opioids [12–14]. It has been suggested that postoperative shivering is perhaps a result of differential recovery of various neuronal centres after discontinuing the anaesthetic—spinal activity recovering earlier than the higher inhibitory centres, resulting in uninhibited spinal activity in the form of rigidity and clonic spontaneous tremor [4, 21, 24, 25]. This theory is substantiated by the successful use of a cerebral stimulant such as methylphenidate, which may enhance recovery of the brain from depression by anaesthetic agents and thereby establish normal control over spinal reflex activity [21]. Sarma and Fry [15] found that doxapram, another cerebral stimulant, was effective in treating postoperative shivering in 73 % of patients. Fifty percent of their patients stopped shivering in less than 1 min after i.v. injection of doxapram 100 mg. In the present study, 85 % of patients treated with doxapram stopped shivering within 10 min of administration. Success rates of 50 % and 75 % occurred at 3 and 5 min, respectively, compared with only 10 % at both times after treatment with saline. Our study confirms the effectiveness of doxapram in treating postoperative shivering, but differs from the earlier study in its time course. We are unable to comment on this difference, as Sarma and Fry [15] did not grade shivering according to severity and their patients may therefore have been different from ours with regard to the severity of shivering at the time of entry into the study.

Doxapram is known to stimulate the respiratory centre, whilst pethidine may cause respiratory depression, although none of our patients had clinically obvious respiratory depression. All of the patients in the study maintained an oxygen saturation greater than 94 %, but all were receiving oxygen via a Hudson mask as a part of their routine care. Doxapram may also transiently increase heart rate and arterial pressure. We did not compare circulatory variables after treatment in the three different groups because of the questionable reliability of non-invasive cardiovascular measurements in shivering patients [11]. However, none of the patients in the doxapram group had a clinically significant episode of hypertension as defined as a diastolic arterial pressure greater than 100 mm Hg.

It is difficult to find an appropriate explanation for the effectiveness of pethidine in treating postoperative shivering. It has been reported as effective in treating shaking chills associated with amphotericin B, and granulocyte and platelet infusions [26]. It has also been shown to control shivering in patients undergoing Caesarean section under extradural anaesthesia, by either i.v. [27] or extradural routes [28]. After general anaesthesia, Claybon and Hirch [13] reported that, after general anaesthesia, pethidine 25 mg arrested shivering within 5 min in 73 % of patients. Later, it was shown to be superior to both morphine and fentanyl in this respect [14]. A more recent study shows that 11 of 14 patients stopped shivering within 5 min after pethidine 25 mg i.v., and that pethidine was effective in reducing the increased metabolic demand of shivering [12]. Our results agree with these studies, in demonstrating the effectiveness of pethidine and suggest that pethidine may be marginally superior to doxapram in this respect. However, in the absence of full dose–response curves to both agents, we have no direct evidence that each drug was administered in optimal doses.

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SPECTRAL CHARACTERISTICS OF EMBOLIC HEART SOUNDS DETECTED BY PRECORDIAL DOPPLER ULTRASOUND DURING VENOUS AIR EMBOLISM IN DOGS

P.-W. LUI, Y.-M. LIN, F. H. Y. CHAN, M.-Y. TSOU, S. WANG, F. K. LAM AND P. W. F. POON

SUMMARY

We have studied the frequency spectrum of embolic heart sounds as detected by precordial Doppler ultrasound after injecting air 0.01–0.1 ml into the external jugular vein of anaesthetized dogs ($n = 7$). At volumes of 0.05 ml and greater, there was a significant increase in both the maximum frequency of the spectrum and the power of those high frequency components to greater than control values. Both changes correlated significantly with the volume of air injected ($P < 0.05$). With repeated injections of air at 5-min intervals, there was a small increase in the high frequency components in the control signal between injections ($P < 0.05$). We conclude that such spectral changes could be used to quantify the volume of air in transit through the heart, and to reflect the short-term history of venous air embolism. (Br. J. Anaesth. 1993; **71**: 689–695)

KEY WORDS

Embolism: venous air. Monitoring: precordial Doppler ultrasound.

Precordial Doppler ultrasound (PDU), a continuous wave Doppler, is used routinely for the detection of venous air embolism during various surgical procedures [1–4]. This method requires the constant attention of an anaesthetist to evaluate subtle changes in the PDU signal. Hence, a sensitive method for the automatic detection of abnormal PDU signals is needed.

More importantly, the conventional PDU method provides poor quantitative information about the volume of air entering the circulation. This information is useful, as the anaesthetist usually acts only when clinically significant volumes of air embolism are present [5]. That spectral changes of Doppler signal may be useful for such quantification was suggested in experimental conditions—for example, in the cerebral artery, air embolism resulted in an increase in high frequency spectral components [6]. The change in spectrum was proportional to the volume of air embolism, presumably reflecting the air bubbles travelling at a speed greater than that of blood [7]. In the case of the heart, where fluid dynamics become complex, the received PDU signal consisted of spectral shifts over a broad frequency range and could display even more complex changes, especially if air bubbles moved at different velocities during the cardiac cycle [8].

At present, the complex spectral changes of the PDU signal associated with controlled injections of air are unknown. As part of a continuing effort to develop a quantitative and automatic PDU system, we have examined the frequency changes in the embolic PDU signal, focusing on the changes at the high frequency end. To characterize the high frequency change of the spectrum, we estimated its maximum frequency ($F\max$) using the percentile-and-threshold crossing method [9], which has demonstrated advantages over similar algorithms. To test the sensitivity of the spectral approach, we used small volumes of air (0.01–0.1 ml) to simulate the condition of subclinical venous air embolism in the dog. The other rationale for using very small volumes of air was to minimize the cumulative effects of air bubbles in the same animal with repeated injections, and to avoid cardiac arrhythmia induced by large volumes of air. Preliminary results have been presented in abstract form [10].

MATERIALS AND METHODS

The study was approved by the Animal Research Committee of the Veterans General Hospital, Taipei. Seven mongrel dogs weighing 10–12 kg were anaesthetized with pentobarbitone 40 mg kg^{-1} i.v. and placed in the supine position. The trachea was intubated with a cuffed tracheal tube and the lungs ventilated mechanically with 100 % oxygen and tidal volume 15–20 ml kg^{-1} (Ohmeda Respirator 7000). Ventilation was adjusted to maintain end-tidal carbon dioxide concentration (E'_{CO_2}) between 4.0 and 5.0 % as detected by an infra-red sensor (Normac, Datex). Cardiac rhythm was monitored by elec-

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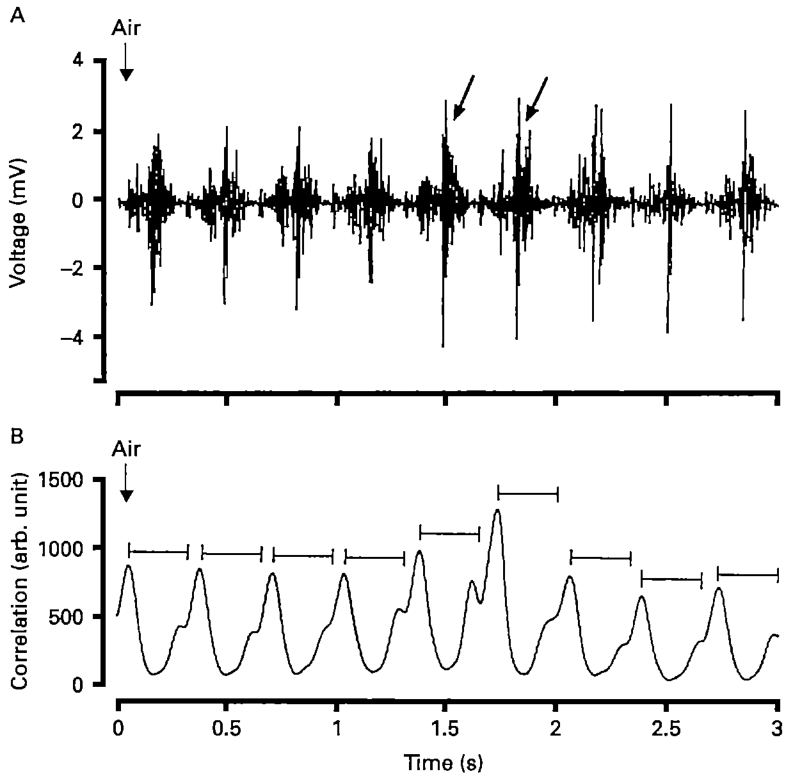

FIG. 1. Method of extracting individual heart beats from the precordial Doppler ultrasound (PDU) signal. A: Time waveform of a continuous record of control Doppler heart sounds (CHS) is shown with embolic heart sounds (EHS, arrows) after injection of 0.01 ml of air. Each cardiac cycle consisted of two bursts of activity, corresponding respectively to an early phase of atrial contraction and a later ventricular systole. B: Cross-correlogram generated by multiplying the signal in A with a template selected from the averaged CHS signals (after removing sign). Individual beats (the first 250 ms of each beat) were identified according to the peak positions in the cross-correlogram (horizontal markers).

trocardiograph (lead II). A 16-gauge Teflon catheter (Arrow International, Reading, PA, U.S.A.) was inserted via the right external jugular vein for air injections. Anaesthesia was maintained with supplements of pentobarbitone 10 mg kg^{-1} h^{-1} i.v. and pancuronium 0.1 mg kg^{-1} i.v. Rectal temperature was controlled at 37 ± 1 °C using a heating lamp, and 0.9% normal saline in glucose solution was infused i.v. at 3 ml kg^{-1} h^{-1} to maintain a constant blood volume.

A generous quantity of coupling gel (Aquasonic 100, Parker Lab., U.S.A.) was applied thoroughly to the face of the Doppler ultrasonic flow transducer (2.4 MHz, Versatone, model P-81, MedaSonic, U.S.A.), which was then placed over the shaved skin at the right lateral border of the sternum and secured around the chest by Micropore tapes. In the MedaSonic, the Doppler circuit amplifies only those velocity components representing forward flow with respect to the probe—the reverse flow is not detected. The correct placement of the transducer over the heart was confirmed by a clearly audible turbulence sound induced by a rapid injection of saline 10 ml into the external jugular vein. The electrical output of the PDU system was recorded first on an audio tape recorder (Sony Professional, Japan), and later digitized at 4-kHz, 12-bit resolution on a Workstation (IBM 386 with a Data Translation Interface board, DT-2801A) for off-line analysis. The overall frequency response of the recording system was flat (±3 dB) from 20 Hz to 18 kHz.

After background PDU signals were obtained at the end of a 15-min stabilization period, air was systematically injected with a microsyringe (100-µl, Hamilton) through a 20-gauge needle inserted into the catheter through the plastic hub of the i.v. giving set. We followed ascending volume steps (0.01, 0.02, 0.05 and 0.1 ml) with a 5-min interval between injections. Air was invariably injected as a quick bolus, and then flushed rapidly into the venous circulation with normal saline 0.5 ml. The ventilator was turned off temporarily during a 20-s period at the time of injections, to minimize respiratory artefacts that could interfere with data collection. For each data segment, 5 s of pre-injection PDU signals (consisting of about 15 heart beats) was recorded to represent control heart sound, followed by the next 15 s of post-injection signals (about 45 beats, which contained the embolic heart sounds). The animal was hyperventilated just before data collection in order to minimize the increase in E'_{CO_2} during recording.

To examine gross changes in the frequency spectrum, we quantified the spectral contents on the basis of "single heart beat" (or single cardiac cycle). We selected the first 10 control heart beats from the raw audio signal and used their full wave rectified average as a template for each of the 20-s data segments. The template (256 m long, 1024 points, non-smoothed) was moved systematically through the full wave rectified peri-injection segment in 5-ms steps while computing for cross-correlation co-

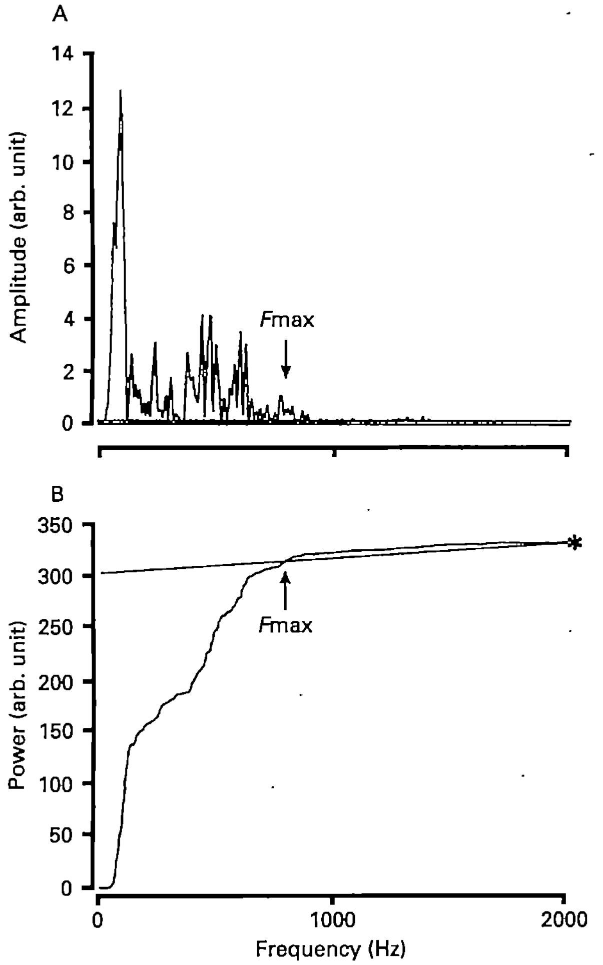

FIG. 2. Estimating *F*max of a spectrum using the hybrid method of percentile-and-threshold crossing. A: Spectrum of a control heart sound (single beat) plotted with its "spectral noise" (3 % of total spectral power, horizontal line next to the *X*-axis). B: Representing the spectrum in A in terms of integrated power (irregular line). The 3 % spectrum is represented here in unit of power/spectral range (inclined line); a common point with the integrated power curve is shown at the asterisk. The *X*-axis of the crossing point (arrow) defines *F*max, where the spectral power of the signal exceeds the background noise from the high frequency end. See text for further details.

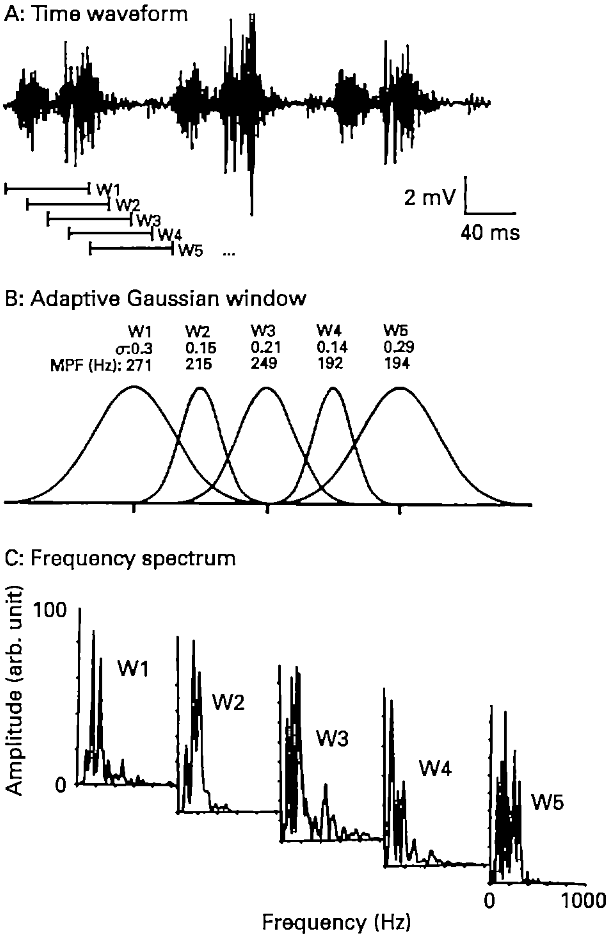

FIG. 3. The Short Time Fourier Transform (STFT) procedure for estimation of the frequency spectrum. A: PDU time waveform showing three consecutive heart beats in relation to the moving windows (horizontal markers, W1, W2...) to be used in the Fast Fourier Transform (FFT). B: Mean power frequency (MPF) values of the spectra extracted with a standard Gaussian window are displayed along with the moving windows. Adaptive Gaussian envelopes are then generated (bell-shaped curves). The width (or sigma value) of each envelope is set according to the rate of change in MPF with respect to its preceding window. C: Corresponding frequency spectra generated by STFT (full display of results is in figure 8).

efficients. The correlogram displayed a series of periodic peaks corresponding to the incidence of individual heart beats (fig. 1). A Gaussian window (sigma = 0.3) was then multiplied with each identified beat and Fast-Fourier Transform (FFT) was performed over those time spans (each of 256 ms, 1024 points) corresponding to the occurrence of individual heart beats.

*F*max of the spectrum was estimated using the hybrid algorithm of percentile-and-threshold crossing [9]. Briefly, the average background signal of the spectral region representing the top 3 % of the entire frequency spectrum was computed first (fig. 2A), then the integrated power profile of the whole spectrum was generated (fig. 2B). The background signal (ratio of spectral energy to spectral band) was overlaid on the integrated spectral profile with a common point at the spectral maximum (fig. 2B, asterisk). The intersection of these two curves represents *F*max on its horizontal axis. *F*max would hence be defined as the frequency at which the PDU signal began to increase to greater than background noise level in the spectrum, as measured from the high frequency end. For a given 20-s data segment, *F*max of the control PDU signal before any air injection was taken as reference for that animal. Spectral power at frequencies greater than this *F*max was defined as the high frequency (HF) component.

To examine finer temporal changes in the frequency spectrum, we used a Short Time Fourier Transform (STFT) (fig. 3). This STFT procedure was necessary because the embolic heart sounds caused by the passage of small air bubbles produced rapid changes in the PDU waveforms and hence represented a non-stationary signal handled poorly by conventional FFT procedures [11]. We varied the width of a Gaussian window according to the "instantaneous" change in the mean power frequency (MPF) of the spectra [12]. This procedure involved two stages of analysis: first, the entire 20-s data segment was partitioned into a series of shorter segments (32 ms, 128 data points), with 5 ms (20 data points) of overlap. For each of these 32-ms segments, a frequency spectrum was obtained (with a fixed Gaussian window; sigma = 0.3), and for each spectrum its MPF was calculated in accordance with the following equation:

$$\text{MPF} = \sum_{f_l}^{f_h} f * P(f) / \sum_{f_l}^{f_h} P(f)$$

where f = frequency; f_l = lower cut-off frequency; f_h = higher cut-off frequency; $P(f)$ = power at a frequency, f.

The second analysis was similar to the first one, except the width of the Gaussian windows was now varied instead of fixed. For each of the 32-ms data segments, the sigma value of the Gaussian window was chosen according to the rate of change in MPF of the segments with respect to each preceding neighbour (sigma = 0.1 × [MPF change] Hz s^{-1}). A rapid change in MPF thus resulted in a narrow window. This procedure had the advantage of minimizing the effects of spectral spreading found in the conventional moving FFT procedure, and allowing the spectral changes to be related to different parts of the cardiac cycle.

The correlation between embolic air volume and change in *F*max or integrated HF components at frequencies greater than control *F*max was then examined for significance by linear regression. Student's *t* test was used whenever appropriate. Results are reported as mean (SEM); $P < 0.05$ was considered significant.

RESULTS

Within the same animal, the spectrum of the control heart sounds before air injections was reproducible (fig. 4A). For the seven animals, the mode of this spectrum was averaged at 128 (SD 40) Hz, which was relatively constant during the course of experiment. The spectral energy occupied the range of frequencies less than 369 Hz which represented their mean *F*max. In the control heart sounds, the beat-to-beat variation in *F*max within the same animal was small (< 10%) compared with the larger range in *F*max across animals (178–451 Hz).

With the smallest volume of air injected (0.01 ml), there were already measurable changes in the frequency spectrum. Typically, *F*max of at least one heart beat was shifted to a higher frequency within the first 2 s after air injection (fig. 4B, C). This change was not observed in the control with an injection of 0.5 ml of saline (the volume of fluid used for flushing the air down the vein).

At volumes of 0.05 ml and greater, the increase in the single beat *F*max greater than control was statistically significant ($P < 0.05$). The correlation between volume of air injected and the greatest single-beat *F*max in the period after injection was significant ($P < 0.01$) (fig. 5).

Concomitant with the increase in *F*max, the integrated power of HF components at frequencies greater than *F*max of the control also increased. With larger volumes of air, such increases in HF could be found in a number of post-injection beats, but lasted usually no longer than 15 beats after the injection (fig. 6). The delayed change in HF of three to six post-injection heart beats was observed consistently at all volumes of air studied, reflecting the circulation time of the air from the external jugular vein to the heart.

The relationship between volume of air injected and the integrated HF components at frequencies greater than control *F*max was studied over the first 15 heart beats (or about 5 s) in the period after injection. We summed all the spectral power at frequencies greater than control *F*max in those beats and plotted the results against the volume of air injected (fig. 7A). The increase in HF components

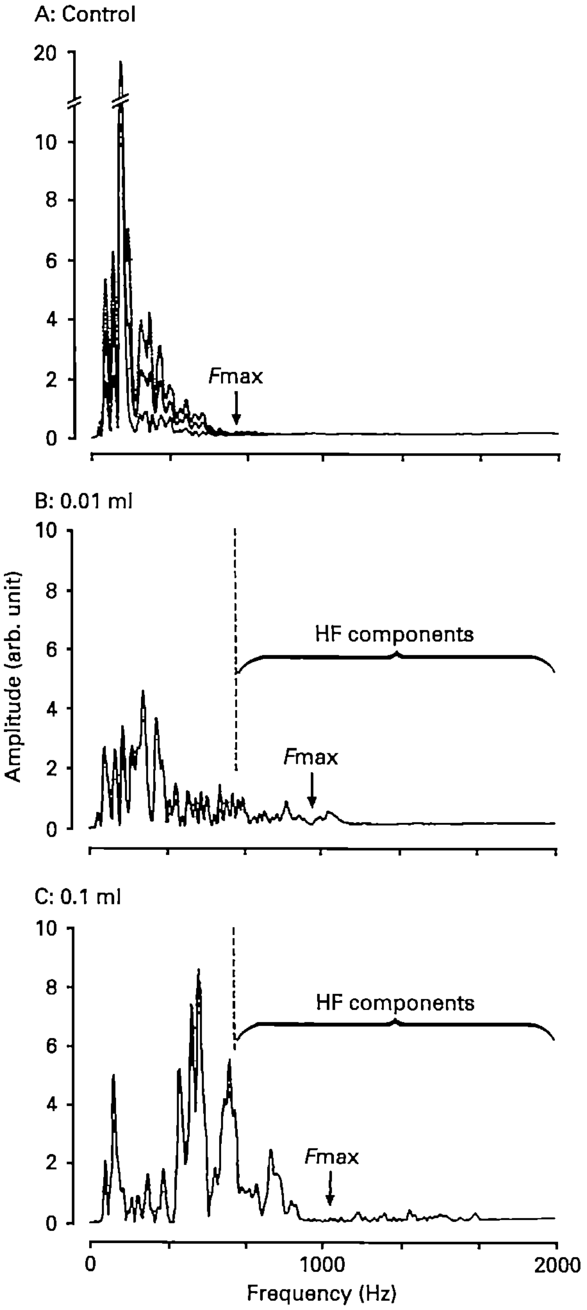

FIG. 4. Typical spectra of PDU signals in a dog showing *F*max (arrows) and high frequency (HF) components. A: Single-beat spectrum of the control PDU signal. Solid line = average of 15 pre-injection beats; dotted line: 1 SD from the mean spectrum. B and C: Typical single-beat spectra of embolic heart sound (EHS) after injection of air 0.01 ml (B) and 0.1 ml (C). Same arbitrary scales.

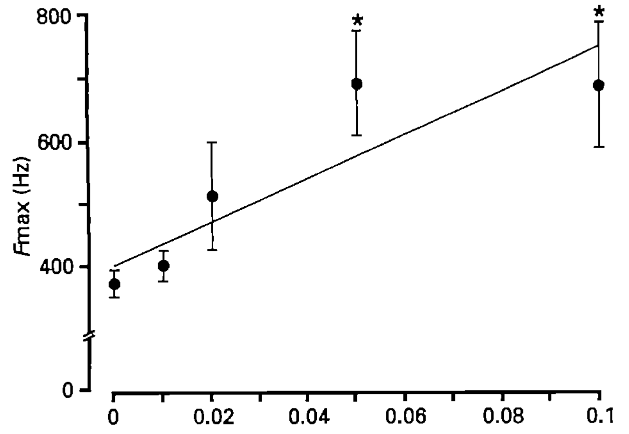

FIG. 5. Relationship between the volume of air injected and the largest value of single-beat *F*max in the period after injection. Each point represents mean (SEM) *F*max at different volumes of injected air (seven dogs). $y = 2833x + 399$; $r = 0.46$. $*P < 0.05$ compared with control.

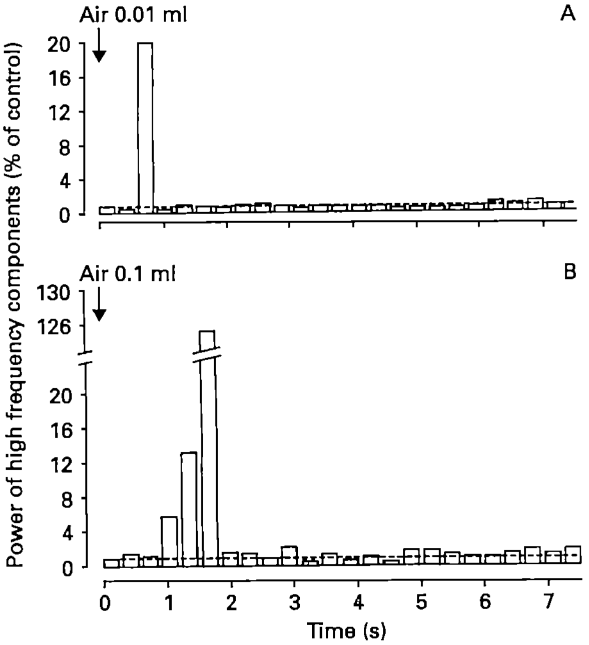

FIG. 6. Time-course of the change in high frequency components after air injection of 0.01 ml (A) and 0.1 ml (B) in a dog. Each bar represents the time of occurrence of a heart beat (*X*-axis) and the integrated power of the HF components (*Y*-axis).

was significant at volumes greater than 0.02 ml ($P < 0.05$). The correlation between the HF components and the volume of air injected was significant also ($P < 0.01$).

From those post-injection beats of the seven dogs, there was a significant correlation between the largest value of the single-beat *F*max and the integrated power of the HF components ($P < 0.01$).

As four successive air injections were given to the same animal within a period of nearly 30 min, there could have been cumulative effects in the spectrum. To examine this, we measured the HF components of 15 heart beats preceding each of the four air injections. Compared with control, there was a smaller increase in the HF components (fig. 7A, dotted line) ($P < 0.05$). Correcting for this cumulative change in the spectrum (by subtracting from each post-injection data point its corresponding pre-injection value), a significant relationship was found between volume of air injected and the increase in integrated power of the HF components ($P < 0.05$) (fig. 7B).

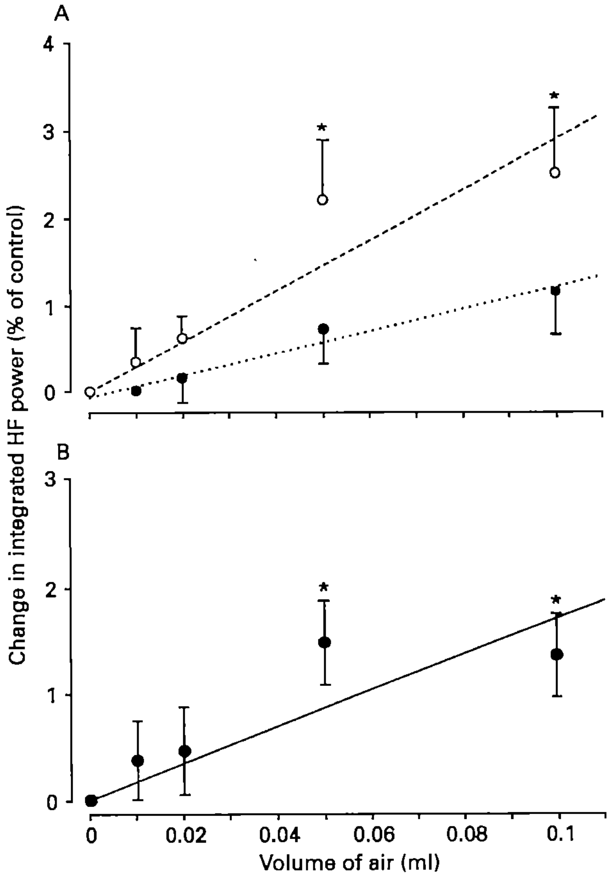

FIG. 7. Relationship between volume of air injected and change in the HF components integrated over 15 heart beats (seven dogs). A: ○ = After injection; ● = before injection. B: Data after injection, as in A, but after subtracting the pre-injection value. $*P < 0.05$ compared with control. See text for details.

We also measured the cumulative effects of air injection on the mean *F*max in the periods before injection. There was a small increase in mean *F*max with repeated air injections, but this relationship was not statistically significant.

With small volumes of air injection, the extra HF components appeared prominently and briefly towards the later part of a cardiac cycle, corresponding with the phase of ventricular systole (fig. 8A–C). At larger volumes (fig. 8D), the increase in HF components was found more extensively throughout the entire cardiac cycle, especially at the initial phase of both ventricular and atrial contractions.

DISCUSSION

We found transient but significant changes in the frequency spectrum of the PDU signals after injections of small volumes of air into the external jugular vein. The spectral changes included an increase in both *F*max and the HF components integrated at frequencies greater than control *F*max. The two changes, which correlated significantly,

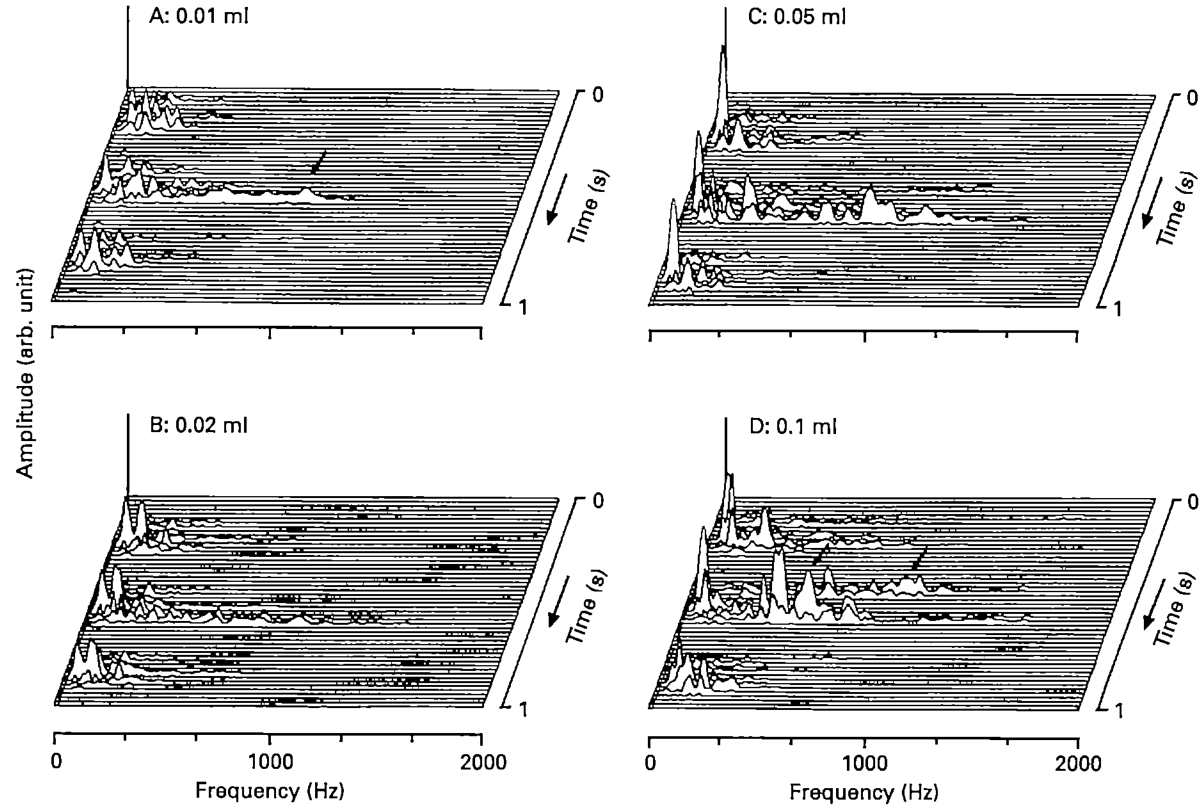

FIG. 8. Time-frequency plots of the EHS in a dog, showing details of spectral changes in the PDU signal at different volumes of injected air. Each panel is a 1-s sample of data showing three consecutive heart beats (the three isolated clusters of spectral peaks). The extra HF components of the EHS occur towards the end of the cardiac cycle, and spread throughout the cycle with increased volume of air (arrows).

probably reflected manifestations of the same phenomenon: an increase in high frequency energy. The integrated power of the HF components appeared to be comparable in sensitivity to that of *F*max, although it was slightly more sensitive in detecting the cumulative venous air embolism.

As air bubbles could be recirculated and could remain inside the heart for a few cycles, the present method of integrating spectral power over the post-injection time may have overestimated the volume of air in transit through the heart, producing some non-linearity in the results.

In further attempts to accurately quantify venous air embolism on the basis of spectral analysis of the PDU signal, one should not ignore individual variations as reflected in the large range of control *F*max values across animals. Using the present method of placing the PDU probe, we may control only the proximity of the probe to the heart, but certainly not the orientation of the probe with respect to the cardiac velocity vector. This could explain the large individual variations in control *F*max across animals. It was interesting to note that the animal in which we observed the clearest change in spectrum was also the one showing the largest control value of *F*max.

The operation of PDU involved two piezoelectric devices—one for continuous transmission of ultrasound, the other for continuous reception of back-scattered signals. With air introduced into the blood stream, because of the large difference in impedance to ultrasounds between air and blood (about 4000-fold) [8], strong reflection of the ultrasonic signal would occur, causing large amplitudes in the reflected spectrum. Particles moving in the PDU field produce an upshift in the Doppler spectrum when their velocity towards the probe is increased [7]. There is no evidence to show to what extent air bubbles may resemble particles travelling in blood but, if they did to some extent, one would expect from Newton's law ($f = ma$) that, because of its lighter mass, air subjected to the same force of the ventricle would be ejected into the pulmonary artery at a speed greater than that of the surrounding blood. This is consistent with our observation that the HF components appeared at high positions in the spectrum and in a transient manner near the ventricular systole, indicating a reflective air–blood interface approaching the ultrasonic probe at great speed. The exact temporal relationship between the appearance of the HF components and the cardiac events needs to be confirmed, however—for example with simultaneous measurement of the blood flow in the pulmonary artery.

Despite obvious differences in organ geometry and fluid dynamics, there is striking similarity in results between the heart and the cerebral artery [6] in terms of the relationship between air injection and HF components. This could be explained by the fluid dynamics common to the cerebral blood vessel and the pulmonary artery.

Using the HF components to detect the passage of air bubbles through the heart or blood vessels proved to be extremely sensitive (to as little as 0.01 ml). In fact, this is as sensitive as the imaging method of transoesophageal Doppler echocardiography (TDE) [4]. In comparison with TDE, spectral analysis has the advantage of being implemented easily as a real-time system (using real-time FFT hardware) for automatic and quantitative detection of the embolic air. TDE is an imaging method that requires more complex data processing, in addition to having a greater cost.

The residual increase in HF components observed in the PDU signals after multiple air injections was surprising as it lasted up to 5 min, even with small venous air emboli. This suggests that air may be trapped for an extended period of time within the heart, perhaps in the form of fine bubbles. This finding on the cumulative effects of air injection may be useful for designing an early alarm system against venous air embolism. The exact time-course of such cumulative effects, especially with larger volumes of air injection when clinical consequences of venous air embolism become important, awaits further study.

It should be pointed out that changes in the PDU signal were not restricted to the high frequency end. The entire spectrum of embolic heart sounds was often altered drastically compared with the control. In the present study, no attempt was made to evaluate the more complex changes in the lower frequency range.

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CARDIOVASCULAR EFFECTS OF ISOFLURANE AND HALOTHANE IN YOUNG AND ELDERLY ADULT PATIENTS

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SUMMARY

We have studied the cardiovascular effects of 1 MAC end-tidal concentrations of halothane and isoflurane in young ($n = 40$) and elderly ($n = 40$) adult patients using non-invasive techniques. Cardiac output was measured by Doppler ultrasonography. Halothane reduced heart rate, systolic, mean and diastolic arterial pressures and cardiac index in both age groups ($P < 0.05$). Isoflurane reduced systolic, mean and diastolic arterial pressures also, but reduced cardiac index and heart rate only in the older patients ($P < 0.05$). Halothane depressed cardiovascular state significantly more than isoflurane in the younger adults ($P < 0.05$), but cardiovascular depression was similar for the two agents in the older age group. The decreases in systolic and diastolic pressures in the older patients were significantly greater with isoflurane compared with halothane ($P < 0.05$). (Br. J. Anaesth. 1993; **71**: 696–701)

KEY WORDS

Anaesthetics volatile: halothane, isoflurane. Heart: cardiac output, Doppler ultrasonography. Age factors.

Volatile anaesthetic agents form the mainstay of general anaesthesia and may be suitable particularly for older patients. They have a good safety record for patients of all ages, are easy to administer and provide a convenient means of varying anaesthetic depth. Unfortunately, in common with i.v. agents, volatile anaesthetics depress the cardiovascular system.

The cardiovascular side effects of both halothane and isoflurane have been well studied in young, healthy volunteers, but there is little information on their effects in an older patient population. Isoflurane has some theoretical advantages for use in older patients because of its low blood solubility [1], the limited extent of its biodegradation [2] and minimal cardiovascular depressant effect [3–5]. Previous work in our department with volatile agents has shown that uptake of halothane, but not of isoflurane, decreased in older adults [6].

In this study we have compared the cardiovascular effects of isoflurane and halothane when given in equipotent doeses to young and elderly adult patients.

PATIENTS AND METHODS

After obtaining University Research Ethics Committee approval and their informed consent, we studied 40 patients aged 60 yr or more and 40 patients aged 20–40 yr, all within 20 % of their predicted lean body mass and ASA I or II. Patients were excluded if they were receiving any cardioactive medication, had recently received halothane or had a history of malignant hyperthermia. Temazepam 10–20 mg was given by mouth 1 h before the study commenced.

Patients were allocated randomly, on a stratified basis for age, to four equal groups of 20 to receive either isoflurane or halothane at the minimum alveolar concentration (1 MAC) in 100 % oxygen for the young and old age ranges (1.15 % or 1.05 % isoflurane; 0.75 % or 0.65 % halothane) according to previous findings [7, 8]. Anaesthesia was induced with etomidate 0.3 mg kg^{-1}, followed by 1-mg increments for initial maintenance. Atracurium 0.5 mg kg^{-1} was given at the same time to facilitate tracheal intubation with a Portex gas sampling tube, 90 s after induction.

Two minutes after intubation (time 0), the volatile agent was introduced in an inspired concentration designed to achieve 1 MAC (end-tidal) within 2 min. Patients' lungs were ventilated to end-tidal carbon dioxide partial pressures of 4.5 kPa (elderly) or 4.8 kPa (young) in order to compensate for age-related differences in the relationship between $P\text{E}_{CO_2}$ and Pa_{CO_2} [6]. Measurements of arterial pressure, heart rate, cardiac output and volatile agent were made at time 0 and every 2 min for 20 min. During this time, the patient remained undisturbed and the inspired volatile agent concentration was adjusted to maintain 1 MAC expired concentration measured by a Datex Normac.

Cardiac output was measured using a Datascope Accucom cardiac output monitor, which uses the Doppler principle to measure blood velocity in the ascending aorta; aortic blood flow is derived by time integration of the velocity profile and this is multiplied by the cross-sectional area of the aorta [9] which is obtained from a nomogram. The measure-

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TABLE I. *Patient characteristics (mean (range or* SD*)) for the four study groups.* * $P < 0.05$ *compared with younger patients (ANOVA)*

	Elderly		Young	
	Isoflurane	Halothane	Isoflurane	Halothane
Sex (M/F)	8/12	11/9	11/9	12/8
Age (yr)	70 (60–85)	72 (61–82)	29 (19–40)	29 (22–39)
Weight (kg)	67 (8.0)	69 (14.2)	70 (15.6)	74 (9.5)
Height (cm)	165 (8.6)*	167 (8.1)*	170 (10.1)	173 (7.7)
Body surface area (m^2)	1.70 (0.13)*	1.75 (0.21)*	1.78 (0.19)	1.85 (0.14)

TABLE II. *Mean (*SD*) drug dosage and ventilation variables for the four study groups receiving the volatile agents in 100% oxygen.* Pi = *Inflation pressure.* * $P < 0.05$ *compared with young patients (ANOVA)*

	Elderly		Young	
	Isoflurane ($n = 20$)	Halothane ($n = 20$)	Isoflurane ($n = 20$)	Halothane ($n = 20$)
Etomidate (mg)	24 (4.7)	25 (5.7)	27 (6.1)	27 (5.0)
Atracurium (mg)	35 (4.3)	37 (8.8)	36 (7.0)	38 (4.5)
Minute volume (litre)	4.83 (0.816)	5.23 (1.219)	5.40 (1.344)	5.25 (0.993)
Tidal volume (ml)	648 (88.1)	665 (101.4)	693 (89.3)	704 (77.5)
Pa_{CO_2} (kPa)	4.8 (0.28)*	4.8 (0.32)*	4.9 (0.35)	5.0 (0.38)
Pi (cm H_2O)	16 (3.3)	16 (3.8)	17 (4.0)	16 (5.4)

ments in this study were taken in duplicate from the suprasternal notch. Baseline measurements of cardiac output, systemic arterial pressure and heart rate were made after a 10-min period of stabilization in the anaesthetic room. Systemic arterial pressure and heart rate were measured by a Datascope Accutorr.

Data were collected on-line, using a BBC microcomputer which was interfaced with the Accucom and the Normac [10]. The computer collected arterial pressure, heart rate and cardiac output information along with other Doppler information from the Accucom and intermittently sampled the volatile agent concentration over a 10-s period from the Normac. The computer calculated peak and trough concentrations of the volatile agent. The Normac–computer system was calibrated with a standard gas before each study. All the data were stored on disk for later retrieval. Cardiac index was calculated for each measurement using a nomogram-derived estimate for body surface area.

Results were analysed using two- or three-factor repeated measures analysis of variance with Dunnett *t* tests for appropriate individual comparisons. Chi-square and Mann–Whitney *U* tests were applied to non-parametric data. Results were considered significant at the 95% level.

Validation study

We undertook a volunteer study using the Datascope Accucom under steady state conditions, with the same investigator, over a 30-min period to assess the reliability of the machine for use as a measuring device. As expected, there was inter-individual variation in cardiac output, but little change in a given individual with time. A coefficient of reliability of 0.993 was obtained for repeated within-patient measurements. This reliability for trending is in agreement with results from other workers [11, 12] and the Doppler technique is now regarded as a reliable method for evaluating acute drug effects [13] or physiological changes [14].

RESULTS

Patient data for the four groups are shown in tables I and II. There were no differences in drug doses administered or mean ventilatory volume and mean peak airway inflation pressure. Pa_{CO_2} at the end of the study was slightly less in the elderly.

Using ANOVA there were statistically significant changes with time in all variables in each group ($P < 0.05$) and between the younger and older age groups ($P < 0.05$). Both age groups receiving halothane developed significant reductions in heart rate over the 20-min study period (tables III, IV) compared with the effects of isoflurane (tables V, VI). Halothane produced a significant decrease in cardiac index from baseline in both age groups over the duration of the study ($P < 0.05$), but only older patients receiving isoflurane showed a similar decrease, contrasting with unchanged values in the young.

The hypotensive effects of isoflurane were more marked in the older patients as demonstrated by disappearance, after 8 min, of the initial significant differences attributable to age. In contrast, age-related differences in diastolic pressure persisted throughout the study period when halothane was used. During isoflurane anaesthesia and after tracheal intubation, younger patients developed a mild tachycardia, in contrast with a more stable heart rate in the elderly group. There were no age-related differences in heart rate during halothane anaesthesia. Cardiac index remained stable in the young during isoflurane anaesthesia, but there was a persistent decline in the older group. In contrast, cardiac index decreased significantly in both age groups during halothane anaesthesia. During admin-

TABLE III. *Mean (95% confidence intervals) cardiovascular measurements in the older age group at baseline (before induction) and every 2 min for 20 min after commencing a 100% oxygen–halothane anaesthetic mixture* (n = 20). **P < 0.05 for multiple range comparisons against baseline value*

	Baseline	Time (min)										
		0	2	4	6	8	10	12	14	16	18	20
Heart rate (beat min^{-1})	74	91*	90*	89*	81*	76	71	70	68	66*	66*	64*
	(5.2)	(6.0)	(5.9)	(5.7)	(5.8)	(5.7)	(4.7)	(5.7)	(4.6)	(4.2)	(3.8)	(3.6)
Systolic arterial pressure (mm Hg)	145	178*	166*	151	142	134	128*	122*	118*	119*	114*	116*
	(11.2)	(13.6)	(12.9)	(11.6)	(9.7)	(11.7)	(9.9)	(9.6)	(9.2)	(8.6)	(8.8)	(8.3)
Diastolic arterial pressure (mm Hg)	85	108*	100*	92	85	80	76	75	74*	70*	70*	69*
	(8.0)	(10.3)	(8.2)	(7.1)	(6.0)	(7.6)	(6.0)	(6.8)	(6.7)	(6.9)	(6.5)	(6.2)
Mean arterial pressure (mm Hg)	112	138*	127*	118	106	99*	97*	95*	91*	89*	87*	88*
	(8.1)	(10.5)	(9.6)	(8.9)	(7.7)	(8.4)	(7.0)	(7.6)	(7.3)	(7.1)	(6.6)	(5.7)
Cardiac index (litre min^{-1} m^{-2})	3.16	3.42	3.46	3.46	3.14	3.24	3.01	2.87	2.81	2.82	2.85	2.67
	(0.573)	(0.674)	(0.571)	(0.568)	(0.418)	(0.481)	(0.504)	(0.393)	(0.391)	(0.376)	(0.425)	(0.292)
SVRI (dyn s cm^{-5} m^{-2})	3197	3606	3241	3024	2917	2690*	2872*	2822	2830*	2806	2650*	2785*
	(560.5)	(674.5)	(611.6)	(505.5)	(456.4)	(463.7)	(472.6)	(414.0)	(454.1)	(480.5)	(418.0)	(392.3)

TABLE IV. *Mean (95% confidence intervals) cardiovascular measurements in the younger age group at baseline (before induction) and every 2 min for 20 min after commencing a 100% oxygen–halothane mixture* (n = 20). **P < 0.05 for multiple range comparisons against baseline value*

	Baseline	Time (min)										
		0	2	4	6	8	10	12	14	16	18	20
Heart rate (beat min^{-1})	74	93*	98*	92*	83*	78	75	75	71	69	68	66*
	(4.7)	(6.7)	(6.2)	(7.3)	(7.2)	(6.7)	(6.3)	(6.2)	(5.7)	(5.8)	(5.6)	(6.2)
Systolic arterial pressure (mm Hg)	126	163*	141*	126	118*	113*	111*	111*	110*	107*	107*	105*
	(6.8)	(9.0)	(7.2)	(6.8)	(5.1)	(5.0)	(5.7)	(5.6)	(5.0)	(5.3)	(5.0)	(5.3)
Diastolic arterial pressure (mm Hg)	68	97*	80*	70	64	62*	60*	58*	57*	58*	56*	55*
	(4.0)	(8.0)	(4.9)	(5.2)	(4.7)	(4.4)	(3.9)	(4.5)	(5.2)	(4.0)	(3.9)	(3.8)
Mean arterial pressure (mm Hg)	93	126*	111*	98	91	88	86	87	84*	85*	84*	82*
	(5.6)	(7.3)	(5.6)	(5.3)	(5.0)	(4.8)	(4.6)	(4.9)	(4.9)	(4.9)	(4.6)	(5.0)
Cardiac index (litre min^{-1} m^{-2})	3.67	4.58*	4.46*	4.21	4.01	3.62	3.40	3.26	3.22*	3.04*	3.10*	2.95*
	(0.460)	(0.516)	(0.473)	(0.388)	(0.327)	(0.382)	(0.354)	(0.361)	(0.240)	(0.266)	(0.255)	(0.259)
SVRI (dyn s cm^{-5} m^{-2})	2157	2232	2073	1932	1885	2040	2140	2221	2140	2294	2261*	2301
	(292.7)	(231.8)	(276.9)	(220.2)	(186.9)	(262.1)	(268.3)	(247.3)	(192.4)	(234.4)	(200.2)	(236.7)

TABLE V. *Mean (95% confidence intervals) cardiovascular measurements in the older age group at baseline (before induction) and every 2 min for 20 min after commencing a 100% oxygen–isoflurane anaesthetic mixture* (n = 20). *P < 0.05 *for multiple range comparisons against baseline value*

		Time (min)										
	Baseline	0	2	4	6	8	10	12	14	16	18	20
Heart rate (beat min^{-1})	73	85*	85*	84*	81*	77	76	74	72	71	71	68
	(5.0)	(6.4)	(5.4)	(5.6)	(5.3)	(5.6)	(5.4)	(5.2)	(5.3)	(5.0)	(5.2)	(5.2)
Systolic arterial	147	186*	160*	144	133*	120*	115*	109*	104*	104*	102*	99*
pressure (mm Hg)	(13.1)	(15.3)	(15.3)	(14.1)	(12.1)	(12.4)	(11.8)	(11.9)	(11.5)	(12.7)	(13.0)	(10.9)
Diastolic arterial	85	108*	94*	84	77	69*	64*	62*	58*	57*	57*	53*
pressure (mm Hg)	(5.8)	(8.4)	(7.6)	(8.0)	(6.3)	(6.6)	(6.8)	(6.4)	(6.9)	(6.9)	(8.2)	(6.9)
Mean arterial	113	144*	122	111	102*	91*	87*	84*	78*	78*	75*	77*
pressure (mm Hg)	(9.0)	(10.3)	(11.2)	(11.1)	(8.8)	(8.3)	(9.1)	(9.4)	(9.0)	(8.9)	(8.7)	(8.4)
Cardiac index	3.33	3.39	3.28	3.23	3.03	2.94	2.85	2.87	2.72	2.56*	2.52*	2.53*
(litre min^{-1} m^{-2})	(0.597)	(0.842)	(0.789)	(0.592)	(0.474)	(0.396)	(0.370)	(0.460)	(0.437)	(0.371)	(0.339)	(0.374)
SVRI (dyn s cm^{-5} m^{-2})	3173	4002	3471	3044	2905	2659	2573	2440	2418*	2645	2574	2604
	(896.6)	(1081.7)	(808.4)	(609.9)	(442.1)	(432.3)	(386.1)	(347.8)	(372.9)	(448.0)	(427.6)	(407.2)

TABLE VI. *Mean (95% confidence intervals) cardiovascular measurements in the younger age group at baseline (before induction) and every 2 min for 20 min after commencing a 100% oxygen–isoflurane anaesthetic mixture* (n = 20). *P < 0.05 *for multiple range comparisons against baseline value*

		Time (min)										
	Baseline	0	2	4	6	8	10	12	14	16	18	20
Heart rate (beat min^{-1})	74	94*	98*	93*	93*	88*	87*	86*	84*	83*	81	79
	(5.0)	(7.7)	(7.3)	(7.3)	(8.0)	(6.5)	(5.4)	(5.2)	(5.1)	(5.9)	(5.4)	(4.9)
Systolic arterial	122	155*	135*	125	119	112	109*	109*	108*	109*	106*	108*
pressure (mm Hg)	(6.3)	(12.7)	(9.0)	(5.4)	(6.6)	(6.5)	(4.9)	(5.7)	(5.4)	(6.0)	(6.4)	(5.5)
Diastolic arterial	72	92*	76	65	63	60*	58*	57*	56*	57*	56*	55*
pressure (mm Hg)	(4.1)	(10.1)	(9.5)	(5.4)	(4.0)	(4.7)	(4.4)	(4.8)	(4.1)	(5.4)	(5.7)	(5.0)
Mean arterial	93	120*	108*	96	90	85	83*	84*	84*	82*	81*	83*
pressure (mm Hg)	(4.1)	(11.2)	(7.1)	(5.0)	(4.5)	(6.0)	(4.8)	(4.8)	(5.2)	(4.9)	(4.9)	(4.6)
Cardiac index	3.58	4.13*	3.98	3.99	4.03	4.01	3.76	3.86	3.73	3.52	3.63	3.52
(litre min^{-1} m^{-2})	(0.431)	(0.630)	(0.460)	(0.475)	(0.459)	(0.404)	(0.370)	(0.450)	(0.327)	(0.318)	(0.356)	(0.352)
SVRI (dyn s cm^{-5} m^{-1})	2248	2581	2295	1989	1886	1715*	1853*	1785*	1799*	1951	1799*	1983
	(374.1)	(629.7)	(394.1)	(274.3)	(270.0)	(231.7)	(236.8)	(243.9)	(153.0)	(256.1)	(191.0)	(290.4)

istration of each volatile agent, the elderly did not increase cardiac output in response to tracheal intubation.

DISCUSSION

Until recently, it has been assumed commonly that results from studies in young, healthy volunteers could be applied without modification to patients in older age groups. However, there is now abundant evidence that the latter respond differently to many drugs [15, 16] and they are known to have a reduced MAC for volatile agents [7, 8, 17].

Our application of the Doppler technique in young adults has produced results similar to those found by other workers for both isoflurane [3] and halothane [18], further validating its use in these circumstances.

It has been reported that cardiac output declines by approximately 1 % yr^{-1} over 30 yr [16, 19]; heart rate also decreases and systolic arterial pressure increases with ageing. The response to hypotension and exercise is less marked [17, 19]. The baroreflex response to a Valsalva manoeuvre is known to be depressed in the elderly, with a greater change in intrathoracic pressure required to produce the same change in heart rate [19, 20]. Both myocardium and vascular smooth muscle of aged animals exhibit reduced responsiveness to catecholamine stimulation [21–23].

Volatile agents, particularly halothane, depress baroreflex function [24–26] and exert a direct depressant effect on myocardial activity by reducing both the amount of calcium release from the sarcoplasmic reticulum and the influx of calcium to activate myofibrils [27–30]. Furthermore, Lynch [31] has demonstrated a difference in the alteration in tension development induced by these two anaesthetic agents and it is suggested that the two agents produce myocardial depression by different mechanisms [32].

Halothane depresses cardiac function in man without a change in peripheral resistance [18, 33–35], but isoflurane apparently maintains cardiac output, perhaps with an increase in sympathetic autonomic activity [4, 5]. Contractility is depressed more by the volatile agents in a failing heart [36] and this may have some bearing on the greater depression of cardiovascular indices in older patients.

Eger and co-workers have shown, in young volunteers, that halothane is a potent myocardial depressant [18] and these findings are now confirmed in an older age group. We propose that, in elderly patients, isoflurane has a cardiac depressant effect similar to that of halothane. This contrasts with previously published work in younger adults indicating that isoflurane preserved cardiac function [3].

The older patients exhibited a relative bradycardia with isoflurane (although less than with halothane) and this probably contributed to the decrease in cardiac output seen in this group. The baroreflex system discussed earlier may contribute to this, as isoflurane was responsible also for a greater reduction in arterial pressure.

This study has shown that elderly patients exhibit generalized cardiovascular depression with both halothane and isoflurane. This finding is not unexpected for halothane, but is at variance with previous findings in healthy younger adults with isoflurane. The reduction in diastolic arterial pressure with isoflurane may affect coronary perfusion pressure to a greater extent than occurs with halothane, suggesting that halothane is preferable in the older patient in respect of its cardiovascular effects.

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DOSE–RESPONSE RELATIONSHIP FOR INHALED NITRIC OXIDE IN EXPERIMENTAL PULMONARY HYPERTENSION IN SHEEP

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SUMMARY

We have examined the effect of inhaled nitric oxide 4–512 p.p.m. in six sheep with pulmonary hypertension induced first with hypoxia and then with 6 μg kg^{-1} of E. coli *endotoxin. A similar dose-dependent reduction in pulmonary artery pressure occurred in pulmonary hypertension induced by hypoxia or endotoxin, with a maximum effect of 25–30% decrease with nitric oxide 64 p.p.m. Increasing the dose to 512 p.p.m. had no further effect. The ED_{50} for inhaled nitric oxide was 39 p.p.m. for pulmonary hypertension induced by hypoxia and 48 p.p.m. for endotoxin-induced pulmonary hypertension. A dose-dependent increase in arterial oxygenation, which reached a maximum with nitric oxide 64 p.p.m., was seen with inhaled nitric oxide after endotoxin infusion. If the toxicity of inhaled nitric oxide can be determined, it may prove useful in the treatment of pulmonary hypertension secondary to the adult respiratory distress syndrome.* (Br. J. Anaesth. 1993; **71**: 702–708)

KEY WORDS

Lung: vasculature. Pharmacology: nitric oxide.

Pulmonary hypertension in the adult respiratory distress syndrome (ARDS) causes right ventricular failure and reduced left ventricular performance [1]. I.v. vasodilators such as nitroprusside, nitrates or prostacyclin reduce pulmonary artery pressures, but are not selective for the pulmonary circulation and so cause unacceptable systemic vasodilatation and hypotension [2, 3]. As i.v. vasodilators act throughout the pulmonary vasculature, they may increase intrapulmonary shunt by overcoming the effect of local hypoxic vasoconstriction, and so worsen the alveolar–arterial oxygen partial pressure difference and reduce arterial oxygenation [2].

Endothelium derived relaxing factor (EDRF) is an endogenous vasodilator which is either nitric oxide or a nitrosylated compound with similar properties [4–6]. Inhaled exogenous nitric oxide causes selective pulmonary vasodilatation, without affecting systemic vascular resistance [7–11]. As nitric oxide is applied only to ventilated alveoli, an increase in shunt should not occur and oxygenation should not be altered.

Previous work using only one or two different doses has shown that nitric oxide is an effective pulmonary vasodilator, but dose–response studies have been performed only in association with pulmonary hypertension induced by a thomboxane analogue [9]. The effect of inhaled nitric oxide on oxygenation in ARDS has been examined at two doses in patients [7], but an animal model of ARDS has not been examined formally. This study was undertaken for three purposes. First, we have determined the dose–response curve for inhaled nitric oxide in the hypoxic sheep model—in particular, to determine if there is maximum effective dose. Second, we have determined the effects of nitric oxide on pulmonary pressures, vascular resistance and oxygenation in an animal model of ARDS. Third, we have compared the dose–response curves of nitric oxide on pulmonary hypertension caused by these different mechanisms.

MATERIALS AND METHODS

The experiments were conducted in accordance with local and governmental regulations concerning animal experimentation. Six Suffolk sheep (mean weight 39 kg, range 36–42 kg) were anaesthetized with pentobarbitone 18 mg kg^{-1}. Anaesthesia was maintained with infusions of pentobarbitone 5–15 mg kg^{-1} h^{-1} and fentanyl 5–25 μg kg^{-1} h^{-1}. Fluid losses were replaced with Hartmann's solution or normal saline. Tracheotomy was performed using an 8-mm i.d. tube, and the lungs were ventilated to an arterial $P\text{CO}_2$ of 4.5–6.0 kPa using a volume preset ventilator (Oxford ventilator, Penlon, Abingdon, U.K.). Oxygen, nitric oxide–nitrogen mixtures and nitrogen were added as required to a reservoir bag and tube attached to the air entrainment port of the ventilator. Inspired oxygen concentrations were monitored using a Servomex paramagnetic oxygen analyser (Taylor Analytics, Crowborough, U.K.). Exhaled gas was passed through a vane respirometer for measurement of tidal volume and then to a 50-litre mixing chamber. Mixed expired and end-tidal carbon dioxide concentrations were measured using an infra-red absorption analyser (Normocap, Datex, Helsinki, Finland).

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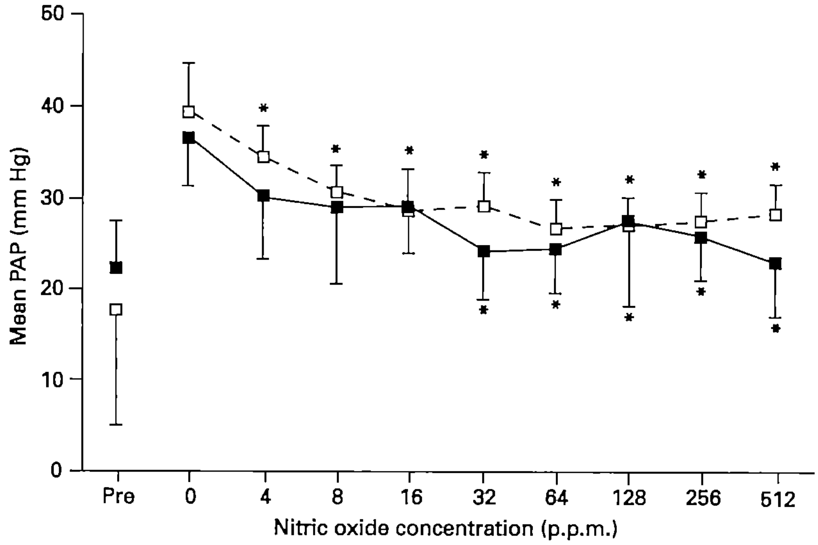

FIG. 1. Effect of inhaled nitric oxide on mean pulmonary artery pressure (PAP) during hypoxia (■) and endotoxaemia (□). Error bars = 1 SD. Pre = Before hypoxia or endotoxin. * Significant difference from baseline (0 p.p.m.) ($P < 0.05$).

A 6-French gauge arterial catheter was placed in the carotid artery and a 7-French gauge balloon-tipped pulmonary artery catheter was passed via the left internal jugular vein. Arterial, pulmonary artery, central venous and pulmonary artery occlusion pressures were measured using pressure transducers calibrated against mercury columns. A COM-2 cardiac output computer (Baxter Healthcare, Santa Ana, California, U.S.A.) was used to determine cardiac output by thermodilution. An ABL330 blood gas analyser and OSM3 co-oximeter (both Radiometer, Copenhagen, Denmark) were used to measure blood-gas tensions and methaemoglobin concentrations.

After initial preparation, the lungs were ventilated using 60% inspired oxygen and the sheep were allowed to stabilize for 30 min. Intravascular pressures, arterial blood-gas tensions, methaemoglobin concentrations and ventilatory variables were recorded. The inspired oxygen concentration was then reduced to 12% by adding nitrogen to the air entrained by·the ventilator, which caused an immediate increase in pulmonary artery pressure. The recordings were repeated and then nitric oxide was added to the inspired gas in concentrations of 4, 8, 16, 32, 64, 128, 256 and 512 parts per million by volume (p.p.m.), the doses being given in random order. Nitric oxide was stored as 2000 p.p.m. in nitrogen (to prevent oxidation to nitrogen dioxide), the flow of the mixture required (8 ml min^{-1} to 1.6 litre min^{-1}) was calculated from the required final concentration and the total ventilation. In greater doses, the amount of nitrogen in the nitric oxide mix caused further reduction in inspired oxygen concentration, which was countered by decreasing the nitrogen flow. Nitric oxide–nitrogen flows were measured and controlled using needle valves and precision flowmeters calibrated for nitrogen (Meterate, Glass Precision Engineering, Hemel Hempstead, U.K. and 1100 series flowmeters, KDG Ltd, Crawley, U.K.). At each dose of nitric oxide, the pulmonary artery pressure stabilized within 5–10 min and recordings were made. The nitric oxide was then stopped and the pulmonary artery pressure allowed to stabilize again. A new set of baseline recordings of intravascular pressures were made before each new dose of nitric oxide.

When all the doses of nitric oxide had been tested, the nitrogen was stopped and oxygen added to the inspired gas to an inspired concentration of 60–80%, to avoid any hypoxic pulmonary vasoconstriction. Endotoxin 6 μg kg^{-1} (from *E. coli* serotype 0127:B8, Sigma, Poole, U.K.) was infused over 30 min. This resulted in a marked increase in pulmonary artery pressure, which remained increased after a small initial decrease when the infusion stopped. The dose–response study with inhaled nitric oxide was repeated, using the same range of doses in a different random order.

The haemodynamic variables (pulmonary vascular resistance, systemic vascular resistance) were derived using standard formulae. The deadspace: tidal volume ratio ($V_D : V_T$) was calculated from the Bohr equation using arterial instead of alveolar $P\text{CO}_2$, after correction of the mixed expired carbon dioxide concentration for changes in water vapour content and temperature. Statistical comparisons were performed using analysis of variance and Duncan's multiple range test with "SPSS for Windows" release 5.0 (SPSS Inc., Chicago, U.S.A.) running under Windows version 3.1 on an 80486-based personal computer. $P \leqslant 0.05$ was taken as statistically significant.

RESULTS

Mean pulmonary artery pressure before hypoxia was 22 mm Hg, increasing to 37 mm Hg after the inspired oxygen was reduced to 12%. Mean pulmonary artery pressure before endotoxin was 18 mm Hg, increasing to 39 mm Hg after endotoxin infusion. Mean pulmonary artery pressure decreased with increasing doses of nitric oxide, but most of the effect occurred between 4 and 64 p.p.m. (fig. 1). There was little additional effect. The SD for the

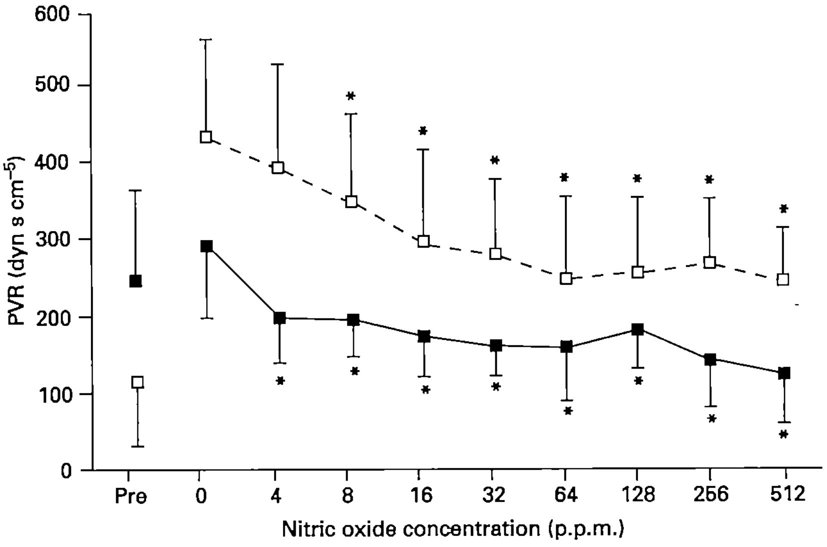

FIG. 2. Effect of inhaled nitric oxide on pulmonary vascular resistance (PVR) during hypoxia (■) and endotoxaemia (□). Error bars = 1 SD. Pre = Before hypoxia or endotoxin. * Significant difference from baseline (0 p.p.m.) ($P < 0.05$).

TABLE I. *Effect of nitric oxide on cardiac output (CO), deadspace:tidal volume ratio* ($V_D:V_T$), *methaemoglobin concentrations (MeHb) and systemic vascular resistance (SVR) (mean (SD))*

	Hypoxia				Endotoxaemia			
Nitric oxide (p.p.m.)	CO (litre min^{-1})	$V_D:V_T$	MeHb (%)	SVR (dyn s cm^{-5})	CO (litre min^{-1})	$V_D:V_T$	MeHb (%)	SVR (dyn s cm^{-5})
Before hypoxia	4.6	0.44	0.6	2017	6.4	0.25	0.7	1001
or endotoxin	(0.6)	(0.1)	(0.1)	(210)	(0.6)	(0.19)	(0.6)	(232)
0	7.5	0.43	0.5	1235	5.2	0.54	0.8	1179
	(1.0)	(0.08)	(0.2)	(197)	(1.1)	(0.06)	(0.2)	(310)
4	7.6	0.36	0.6	1111	5.0	0.55	1.5	1259
	(1.4)	(0.06)	(0.2)	(204)	(1.5)	(0.04)	(1.0)	(434)
8	6.8	0.39	0.9	1184	4.9	0.51	1.5	1337
	(1.4)	(0.08)	(0.3)	(297)	(1.5)	(0.05)	(0.9)	(274)
16	7.7	0.36	0.8	986	5.1	0.51	1.8	1366
	(1.2)	(0.06)	(0.2)	(237)	(1.5)	(0.05)	(0.9)	(692)
32	7.2	0.36	1.2	1153	5.4	0.49	1.5	1286
	(0.8)	(0.07)	(0.4)	(176)	(1.9)	(0.06)	(1.0)	(513)
64	7.4	0.26	1.1	1218	5.1	0.46	1.8	1361
	(1.5)	(0.12)	(0.5)	(512)	(1.2)	(0.05)	(1.0)	(569)
128	6.4	0.38	0.9	1152	5.2	0.48	2.3	1227
	(0.6)	(0.1)	(0.4)	(313)	(1.5)	(0.08)	(1.2)	(425)
256	7.8	0.29	1.7	1096	5.1	0.51	2.2	1212
	(1.0)	(0.14)	(0.5)	(424)	(1.4)	(0.05)	(1.1)	(419)
512	7.2	0.3	1.7	1079	5.7	0.46	2.2	1133
	(0.4)	(0.15)	(0.5)	(477)	(1.7)	(0.09)	(1.1)	(228)

mean pulmonary artery pressure after endotoxin were much smaller than those during hypoxia (coefficients of variation for endotoxin 9–13%, for hypoxia 15–34%) because endotoxin produced a more stable increase in pulmonary artery pressure than hypoxia, with less within- and between-subject variability. The increase in pulmonary artery pressure caused by hypoxia was reversed almost totally by nitric oxide, but the increase caused by endotoxin could not be reversed fully. The ED_{50} (dose of nitric oxide required to produce 50% of maximal percentage reduction in pulmonary artery pressure) calculated from the pooled data was 39 p.p.m. for hypoxia and 48 p.p.m. for endotoxaemia.

The effect of inhaled nitric oxide on pulmonary vascular resistance (PVR) is shown in figure 2. The values for pulmonary vascular resistance before hypoxia and endotoxin were 236 and 119 dyn s cm^{-5}, respectively. The increase in pulmonary vascular resistance caused by endotoxin was not reversed fully by nitric oxide, but even the smallest dose (nitric oxide 4 p.p.m.) was able to reverse the pulmonary vascular resistance increase caused by hypoxia. The decrease in pulmonary vascular resistance to less than the pre-hypoxic baseline was probably caused by the marked increase in cardiac output that occurred with hypoxia (table I).

Cardiac output was unchanged by inhaled nitric oxide both during hypoxia and after infusion of endotoxin (table I). This implies that dose-dependent changes in pulmonary artery pressure and pulmonary vascular resistance are an effect of nitric

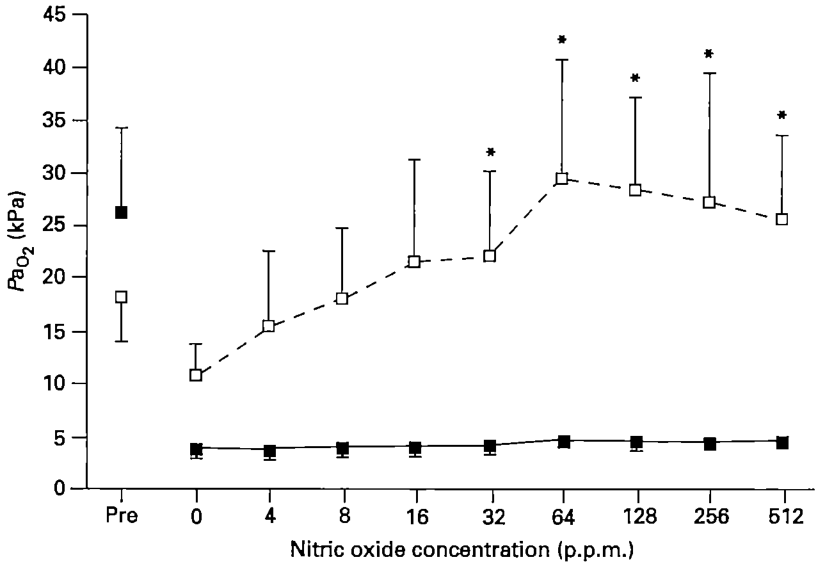

FIG. 3. Effect of inhaled nitric oxide on arterial oxygen partial pressure (Pa_{O_2}) during hypoxia (■) and endotoxaemia (□). Error bars = 1 SD (SD for data during hypoxia are in general smaller than the plotting symbols). Pre = Before hypoxia or endotoxin. * Significant difference from baseline (0 p.p.m.) ($P < 0.05$).

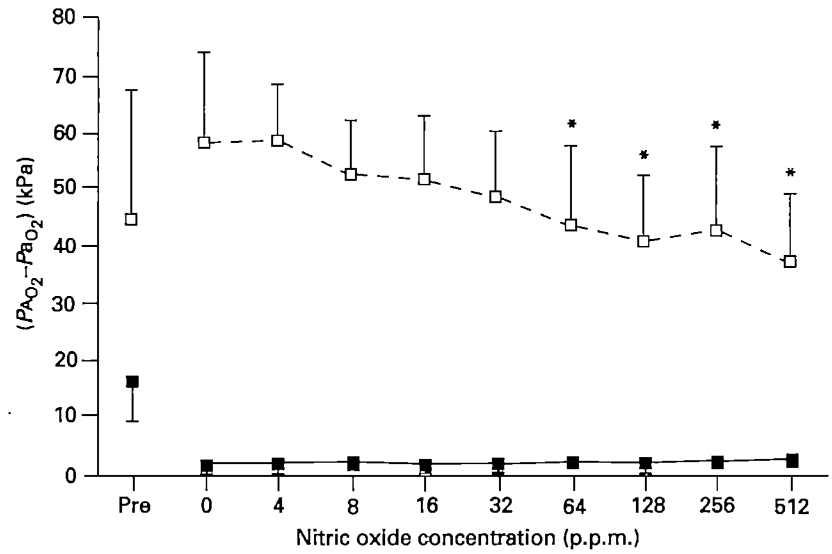

FIG. 4. Effect of inhaled nitric oxide on alveolar–arterial oxygen partial pressure difference ($PA_{O_2}-Pa_{O_2}$) during hypoxia (■) and endotoxaemia (□). Error bars = 1 SD (SD for data during hypoxia are smaller than the plotting symbols). * Significant difference from baseline (0 p.p.m.) ($P < 0.05$).

oxide on pulmonary vasculature and not secondary to altered cardiac output. $V_D:V_T$ and systemic vascular resistance were unchanged by nitric oxide.

After infusion of endotoxin there was a dose-dependent increase in Pa_{O_2} up to 64 p.p.m.; after this there was no further increase (fig. 3). Nitric oxide had no effect on the hypoxaemia caused by 12% oxygen. The inspired oxygen partial pressure during the endotoxin studies varied slightly between sheep (60–80%). Figure 4 shows the alveolar–arterial oxygen partial pressure difference which corrects for this; there is a dose-dependent decrease up to 64–128 p.p.m.

The maximum methaemoglobin concentration observed was 3.7%, and the mean values increased with increasing dose of nitric oxide (table I). It was apparent that the increase in methaemoglobin concentration was both time- and dose-dependent. In one animal, nitric oxide 512 p.p.m. was given for 20 min at the end of the experiment and the methaemoglobin concentration increased linearly with time to 11%. The onset of pulmonary vasodilatation was rapid—within one breath with the greater doses. Reversal of this effect after the nitric oxide was discontinued occurred at 5–10 min.

DISCUSSION

Nitric oxide is a colourless gas formed by combustion in a reducing atmosphere. It is present in concentrations of up to 9 p.p.m. in atmospheric air [12] and in concentrations of up to 1000 p.p.m. in cigarette smoke [13]. Endogenous nitric oxide is synthesized from L-arginine by nitric oxide synthases in mammalian endothelial cells [14], macrophages [15] and nerve tissue [16]. Synthesis may be blocked by N^{G}-

monomethyl arginine or other false substrates and cells deficient in L-arginine release reduced amounts of nitric oxide [17]. It is highly lipid soluble and diffuses rapidly from the endothelium into vascular smooth muscle. Nitric oxide activates intracellular soluble guanylate cyclase [18], increasing intracellular cyclic guanosine monophosphate which, in turn, inhibits calcium release from the sarcoplasmic reticulum and inhibits calcium entry through receptor-operated channels. This causes relaxation of smooth muscle [18].

Nitric oxide is inactivated by combination with haemoglobin with the formation of methaemoglobin. Nitric oxide binds to haemoglobin with an affinity 1500 times that of carbon monoxide [19]; thus nitric oxide which enters the vascular lumen is inactivated rapidly. This accounts for the selective pulmonary vasodilatation seen with inhaled nitric oxide, which presumably acts on the luminal surface of pulmonary vessels. Any nitric oxide entering the blood is inactivated and so does not cause systemic effects. Cigarette smoke, which contains nitric oxide up to 1000 p.p.m., is known to cause pulmonary vasodilatation [20]. These properties of inhaled nitric oxide were first demonstrated by Higenbottam and colleagues [21] in patients with primary pulmonary hypertension. Inhaled nitric oxide has been shown also to cause pulmonary vasodilatation in humans with pulmonary hypertension resulting from mitral valve disease [22], ARDS [7], hypoxia [23] and in neonates with primary pulmonary hypertension of the newborn [24, 25].

In animal models, inhaled nitric oxide has reduced or reversed pulmonary vasoconstriction caused by hypoxia [9], heparin-protamine reaction [10], a thromboxane analogue [9], and infusion of endotoxin [11]. Dose-response data for the reduction of pulmonary artery pressure have been presented for inhaled nitric oxide in lambs using thromboxane analogue-induced pulmonary vasoconstriction [9, 10]. These data suggest that a maximum effect would be reached at about 80 p.p.m., but greater doses were not used. Frostell and colleagues showed also that inhalation of nitric oxide 80 p.p.m. for 6 min had no effect on pulmonary or systemic haemodynamics of animals with normal lungs breathing 60–70% oxygen [9]. Archer and co-workers, using an isolated perfused rat lung model, showed that nitric oxide injected in solution into the pulmonary artery produced a transient, dose-dependent reduction in hypoxic pulmonary vasoconstriction [26].

We are unaware of any formal dose-response studies of inhaled nitric oxide in the hypoxic sheep or in an endotoxin-induced ARDS model in sheep. We therefore sought to confirm existing evidence that nitric oxide reduces hypoxic pulmonary vasoconstriction in a dose-dependent fashion and that there is a greater useful dose beyond which further vasodilatation does not occur, and to see if the same effect occurred in the endotoxic sheep model of ARDS.

Our methods were similar to those of previous studies. The hypoxia induced in our sheep ($F\text{I}_{\text{O}_2}$ 0.12) was not as severe as that used by Frostell and colleagues [9] ($F\text{I}_{\text{O}_2}$ 0.06–0.08), yet it caused a marked increase in both pulmonary artery pressure and cardiac output. We tried initially to reduce $F\text{I}_{\text{O}_2}$ to 0.1, but two sheep showed signs of myocardial ischaemia on ECG, therefore a greater $F\text{I}_{\text{O}_2}$ was used. Endotoxaemia produces a biphasic response in the sheep pulmonary circulation [27]: a brief initial phase of marked pulmonary hypertension is followed by a phase of less severe hypertension and abnormal microvascular permeability. A dose of endotoxin 6 μg kg^{-1} was chosen on the basis of previous (unpublished) work which showed sustained and reasonably constant pulmonary hypertension over many hours after administration. Endotoxin produces an acute model of ARDS with an increased alveolar-arterial oxygen partial pressure difference, microvascular permeability and lung water, but cannot mimic long-term changes such as fibrosis.

Nitric oxide caused a dose-dependent reduction in the mean pulmonary artery pressure that was similar during hypoxia and after endotoxin, with a maximum effect produced with 128 p.p.m. and no significant change thereafter. The ED_{50} values were similar. There would thus be no reason to use doses greater than 128 p.p.m., as maximum pulmonary vasodilatation would have been achieved, while toxicity, as determined by methaemoglobin concentrations, would continue to increase with greater doses. The decrease in pulmonary vascular resistance that occurred with increasing doses of nitric oxide showed a similar pattern.

The pulmonary vasodilatory effect of inhaled nitric oxide was seen with concentrations of nitric oxide 4 p.p.m., confirming its potency in small doses [8–10, 24]. A dose of 4 p.p.m. represents an inhaled dose of about 0.8 μg kg min^{-1} and, if equilibrated with extracellular fluid, would be a 12–13 nmol litre^{-1} solution. Ambient concentrations of nitric oxide in air may exceed this value: up to 9 p.p.m. has been detected as an air pollutant [12]. Nitric oxide was also very specific in effect: no changes in systemic vascular resistance were detected, even with the greatest dose.

In ARDS, systemically administered vasodilators cause an increase in alveolar-arterial oxygen partial pressure difference [2, 3], presumably by vasodilating vessels that are constricted by local hypoxia and so perfusing underventilated areas. It was expected that inhaled nitric oxide would have no effect on arterial oxygenation after endotoxin administration—the nitric oxide simply would not reach underventilated areas. Instead, a dose-dependent improvement in alveolar-arterial oxygen partial pressure difference and arterial oxygenation was noted, with a plateau at 128 p.p.m. and greater and the decrease in pulmonary artery pressure was correlated with the decrease in alveolar-arterial difference ($r = 0.54$, $P < 0.0005$; linear regression). Mean Pa_{O_2} increased by a factor of almost three. This must represent an improvement in the ventilation-perfusion relationships within the lung, presumably as a result of redistribution of blood flow. A study in patients with ARDS using the multiple inert gas elimination technique has also suggested that this occurs [7]. The nitric oxide had no measurable effect on arterial oxygenation during the administration of hypoxic gas mixtures, but the alveolar–arterial oxygen partial pressure difference was so small that there was no room for improvement.

The toxicity of nitric oxide has been reviewed extensively elsewhere [10]. Nitric oxide binds to haemoglobin, forming methaemoglobin and a small amount of nitrosyl haemoglobin [28]. Methaemoglobin is reduced back to haemoglobin and nitrates mostly by NADH–methaemoglobin reductase and the reduction of normal methaemoglobin production uses only a fraction of the capacity of this pathway [29]. When methaemoglobin production is increased by inhaling nitric oxide, this extra capacity is used. Although the maximum methaemoglobin concentration in these experiments did not exceed 3.7 %, the exposure at each dose was only about 15 min; longer exposure of one animal showed a linear increase in methaemoglobin concentration with time. More work is required to determine the dose–time–methaemoglobin concentration relationship. For long term studies, methaemoglobin may not be a suitable marker of nitric oxide toxicity. Mice exposed to nitric oxide 10 p.p.m. for 2 weeks had normal methaemoglobin concentrations, but had signs of increased red cell turnover, with splenomegaly and increased bilirubin concentrations [30].

Gaseous nitric oxide is oxidized to nitrogen dioxide in the presence of oxygen at a rate determined by the oxygen concentration and the square of the nitric oxide concentration [31]. With the greatest concentrations of nitric oxide and oxygen used in this study, 25 % oxidation would be expected to occur in about 1 min; with nitric oxide 4 p.p.m. during hypoxia this would take 12 h. The nitric oxide–nitrogen mix was added to the inspired gas at the point closest to the animal in the ventilation system that would ensure even mixing. The dwell time for the mixture in the ventilation system was short (10 s), so it would seem unlikely that there was significant oxidation of the nitric oxide.

In summary, we have presented data showing that inhaled nitric oxide is a potent and selective pulmonary vasodilator, with a similar dose–response relationship for pulmonary hypertension caused by hypoxia or endotoxaemia. The maximum effect occurs between 64 and 128 p.p.m.; no benefit was found with greater doses. A previously unreported dose-dependent decrease in alveolar–arterial oxygen partial pressure difference was found during nitric oxide inhalation in endotoxaemia. Provided inhaled nitric oxide can be shown to be free of serious toxicity, it may prove useful in the treatment of pulmonary hypertension complicating ARDS.

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British Journal of Anaesthesia 1993; 71: 709–714

DOSE–RESPONSE RELATIONSHIPS FOR EDROPHONIUM AND NEOSTIGMINE ANTAGONISM OF MIVACURIUM-INDUCED NEUROMUSCULAR BLOCK

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SUMMARY

We have studied the dose–response relationships for neostigmine and edrophonium during antagonism of neuromuscular block induced by mivacurium chloride. Sixty-four ASA group I or II adults were given mivacurium 0.15 mg kg^{-1} during fentanyl–thiopentone–nitrous oxide–isoflurane anaesthesia. Train-of-four stimulation (TOF) was applied to the ulnar nerve every 10 s, and the force of contraction of the adductor pollicis muscle was recorded. When spontaneous recovery of first twitch height reached 10% of its initial control value, edrophonium 0.1, 0.2, 0.4, or 1 mg kg^{-1} or neostigmine 0.005, 0.01, 0.02, or 0.05 mg kg^{-1} was administered by random allocation. Neuromuscular function in another 16 subjects was allowed to recover spontaneously. Spontaneous recovery from 90% mivacurium block to 95% twitch height and TOF ratio 0.75 occurred within 15 min. This study demonstrated that the dose–response curves for these two drugs for antagonism of neuromuscular block (first twitch and train-of-four ratio) were parallel. The doses of neostigmine required to achieve 50% (ED$_{50}$) and 70% (ED$_{70}$) recovery of the first twitch after 10 min were 2 (1.5–2.5) µg kg^{-1} and 4.7 (4.1–5.4) µg kg^{-1} (mean (95% confidence intervals)), respectively. Corresponding ED$_{50}$ and ED$_{70}$ values for edrophonium were 2.8 (0.75–10.2) µg kg^{-1} and 9.2 (3.6–23.6) µg kg^{-1}, respectively. These values corresponded to neostigmine:edrophonium potency ratios of 1.4 (0.4–2.4) and 1.95 (0.9–2.9) for first twitch ED$_{50}$ and ED$_{70}$ height, respectively. The calculated doses producing 50% (ED$_{50}$) recovery of the TOF ratio at 10 min were neostigmine 2.57 (1.8–3.6) µg kg^{-1} and edrophonium 26.9 (14.6–49.6) µg kg^{-1}. These values corresponded to a potency ratio of 10.4 (0.7–20). (Br. J. Anaesth. 1993; **71**: 709–714)

KEY WORDS

Antagonists, neuromuscular relaxants: edrophonium; neostigmine. Monitoring: train-of-four. Neuromuscular relaxants: mivacurium chloride.

Mivacurium chloride is a newly developed bisbenzylisoquinolinium non-depolarizing neuromuscular blocking agent. It has a short duration of action in experimental animals [1] and in humans [2, 3]. It is hydrolysed by butyrylcholinesterase (plasma cholinesterase) at a rate 70–88% of that of suxamethonium [1, 4]. As both this enzyme and acetylcholinesterase are inhibited by anticholinesterase drugs, Savarese and colleagues [1] have expressed some concern regarding the effect of cholinesterase inhibitors on the antagonism of mivacurium-induced neuromuscular block. Cook and colleagues [5] reported that the recovery index from mivacurium-induced block was shortened by administration of either neostigmine or edrophonium. They noted, however, that neostigmine in clinically relevant concentrations significantly inhibits the metabolism of mivacurium *in vitro*. In contrast, edrophonium and suxamethonium have no effect on the *in vitro* metabolism of mivacurium [5]. Although it has been suggested that the inhibition of the cholinesterases by edrophonium occurs by a mechanism different than that of neostigmine [6], observations reported by several investigators [5, 7] strongly support the contention that edrophonium does not inhibit butyrylcholinesterase. Therefore edrophonium may be the preferred antagonist of mivacurium block. Further, it has been suggested that anticholinesterase drugs may have effects other than inhibition of acetylcholinesterase at the neuromuscular junction [8, 9].

The dose–response relationships for edrophonium and neostigmine after mivacurium have not been studied. Therefore, this study was designed to establish dose–response relationships for edrophonium and neostigmine as antagonists of mivacurium-induced neuromuscular block.

PATIENTS AND METHODS

After obtaining institutional approval and informed consent, we studied 80 ASA group I or II patients of both sexes, aged 18–52 yr (mean 32.4 yr) and weights 45–90 kg (mean 68.2 (SD 11.3) kg). All patients were undergoing elective procedures, had no neuro-

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muscular, renal or hepatic disease, and were not taking any drug known to interfere with neuromuscular function. All patients received oral lorazepam 2 mg 90 min before operation. An infusion of lactated Ringer's solution was given i.v. before induction of anaesthesia. ECG, pulse oximetry and arterial pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5 ± 0.5 °C. Anaesthesia was induced with fentanyl 2 μg kg^{-1} and thiopentone 3–5 mg kg^{-1}, and was maintained with 70 % nitrous oxide and 0.5–1 % inspired isoflurane in oxygen. Concentrations of isoflurane, nitrous oxide, oxygen and carbon dioxide were measured continuously by a multiple-gas analyser (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal partial pressure of carbon dioxide ($P\text{E}'_{CO_2}$) 4.6–5.3 kPa).

The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 10 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer International, Odense, Denmark). Preload tension on the thumb was maintained at 300 g throughout the investigation. After a stable neuromuscular response was obtained, the patient received mivacurium 0.15 mg kg^{-1} i.v. as a free-flowing bolus dose. Tracheal intubation was performed when neuromuscular response was abolished. Additional increments of mivacurium 0.1 mg kg^{-1} were given to patients who required continued neuromuscular block, whenever the first twitch recovered to 10 % of control value.

At the end of surgery, when first twitch height (T1) (the first response in the TOF) had recovered to 10 % of control value, the patients received edrophonium 0.1, 0.2, 0.4 or 1 mg kg^{-1}, neostigmine 0.005, 0.01, 0.02 or 0.05 mg kg^{-1} ($n = 8$ in each), or no antagonist drug ($n = 16$), by random allocation. Each dose of each antagonist agent was given to eight patients. Atropine, 0.3–1.5 mg, was administered when appropriate. No other antagonist was given for at least 10 min and the inspired isoflurane concentration was not altered. The TOF ratio (the amplitude of the fourth evoked response as a fraction of the first evoked response: T4/T1) was recorded continuously over the subsequent 10 min, at which point the dose–response study was concluded. Eight patients in the group who received no antagonist were allowed to recover spontaneously to a TOF ratio of 0.75. In all other patients, an additional dose of antagonist was given after 10 min if the TOF ratio was less than 0.75 or if the patient had clinical signs of inadequate neuromuscular function.

The results were subjected to probit transformation using PCNONLIN version 4.1 (ClinTrials, Inc., Lexington, Kentucky) [10]. Dose–response

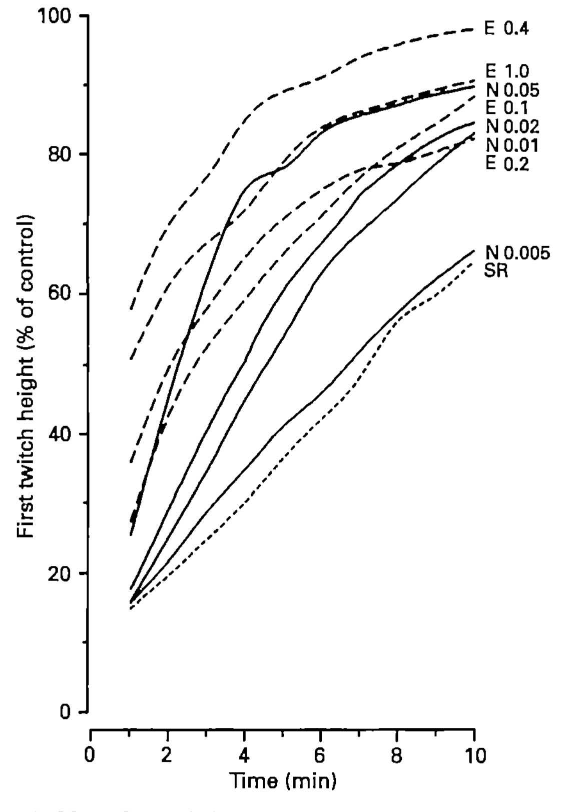

FIG. 1. Mean first twitch height *vs* time after administration of various doses (mg kg^{-1}) of neostigmine (N) (——), edrophonium (E) (—) or in the spontaneous recovery group (SR) (—). Antagonism of neuromuscular block was attempted when first twitch height reached 10 % of its control value. Confidence intervals have been omitted for the sake of clarity.

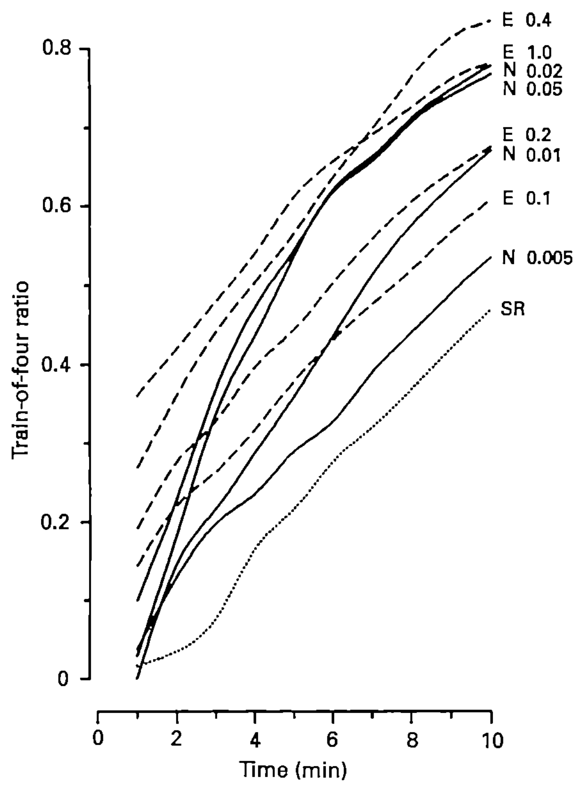

FIG. 2. Mean train-of-four ratio *vs* time after administration of various doses of neostigmine (N) (——), edrophonium (E) (—) or in the spontaneous recovery group (SR) (...). Antagonism of neuromuscular block was attempted when first twitch height reached 10 % of its control value. Confidence intervals have been omitted for the sake of clarity.

TABLE I. *First twitch (T1) and train-of-four (TOF) recovery from 10% block (mean (95% confidence intervals)).* *$P < 0.01$ *compared with the spontaneous recovery group*

Group	n	T1 at 10 min (% control)	TOF ratio at 10 min	Times to T1 recovery (min)					Time to TOF = 0.75 (min)
				n	25–75 %	n	10–95 %	n	
Spontaneous recovery group	16	65 (54.9–75.1)	0.48 (0.42–0.53)	15	9.7 (7.6–11.8)	11	15.7 (12.2–19.2)	8	15.4 (12.7–18.1)
Edrophonium ($mg\ kg^{-1}$)									
0.1	8	88 (78–98)*	0.61 (0.47–0.74)	8	5.2 (3.61–6.79)*	4	8.3 (6.6–10.1)*	2	9.3 (6.6–12)*
0.2	8	82 (67–97)	0.68 (0.56–0.79)*	5	3.8 (0.94–6.6)*	3	4.7 (1.2–8.2)*	4	8.9 (7.6–10.2)*
0.4	8	98 (94–100)*	0.84 (0.75–0.93)*	8	2.8 (1.04–4.6)*	7	5.2 (2.9–7.4)*	5	6.9 (5.3–8.5)*
1.0	8	91 (80–100)*	0.78 (0.66–0.89)*	8	4.8 (1.8–7.8)*	5	5.6 (3.1–8.1)*	6	5.9 (4.2–7.6)*
Neostigmine ($mg\ kg^{-1}$)									
0.005	8	66 (56.8–75.2)	0.54 (0.47–0.60)	3	6.7 (5.5–7.9)*	0	—	0	—
0.01	8	83 (68.8–97.2)	0.67 (0.53–0.81)*	7	5.4 (3.9–6.9)*	3	8.5 (2.8–14.2)	3	7.0 (5–8.9)*
0.02	8	85 (74.1–95.9)	0.78 (0.68–0.88)*	6	5.5 (4.4–6.7)*	2	9.4 (6.7–12.1)	6	7.5 (5.9–7.1)*
0.05	8	90 (75–100)*	0.77 (0.69–0.85)*	7	3.5 (2.1–4.9)*	5	5.4 (2.8–8)*	5	8.1 (6.4–9.8)*

relationships were calculated by linear regression of the probit transformation of T1 and TOF ratio on the logarithm of the dose. From these, the doses of antagonist expected to produce 50% and 70% recovery (ED_{50} and ED_{70}) of T1 and TOF ratio were obtained every 1 min for 10 min after the administration of the drug. Regression lines were compared using analysis of covariance. First, we tested the lines to determine if they deviated from parallelism; if they did not, an F test was applied to determine if the elevations were different. If so, a t test was applied to determine which line differed in elevation [11], using BMDP statistical package (University of California Press, 1990). Comparisons were made between the potencies of the antagonist drugs [12]. Recovery times of the first twitch from 25 to 75% and from 10 to 95% were compared using analysis of variance. Dunnett's test was used to compare the spontaneous recovery group to each of the other groups. Results were expressed as means and 95% confidence intervals, and were considered statistically significant when $P \leqslant 0.01$.

RESULTS

Figures 1 and 2 show first twitch height and train-of-four ratio as a function of time after administration of the antagonist. At all doses, the effect of edrophonium was rapid and sustained; neostigmine had a slower onset. The largest doses of either edrophonium (1.0 $mg\ kg^{-1}$) or neostigmine (0.05 $mg\ kg^{-1}$) did not result in the greatest recovery of T1 or the TOF ratio, 10 min after antagonism (table I). The differences in recovery characteristics observed with edrophonium 1.0 $mg\ kg^{-1}$ compared with 0.4 $mg\ kg^{-1}$, or neostigmine 0.05 $mg\ kg^{-1}$ compared with 0.02 $mg\ kg^{-1}$ were not statistically significant ($P > 0.05$).

First twitch recovery 10 min after antagonism was greater ($P < 0.01$) in those patients who received edrophonium 0.1, 0.4 or 1.0 $mg\ kg^{-1}$ or neostigmine 0.05 $mg\ kg^{-1}$ than in those allowed to recover spontaneously (table I). Similar observations were noted for TOF recovery (table I). Similarly, time for the twitch height to recover from 25 to 75% and from 10 to 95% of the control value was significantly greater in the spontaneous recovery group compared with other groups (table I). In the absence of antagonist, the mean time required to attain a TOF ratio of 0.75 in the spontaneous recovery group was 15.4 (12.7–18.1) min. This was greater ($P < 0.01$) than times in other groups who received the antagonist agent (table I). It should be noted that not all patients who received anticholinesterase drugs recovered to a TOF ratio of 0.75 at 10 min, and none of the patients in the group who received neostigmine 0.005 $mg\ kg^{-1}$ had recovered to TOF of 0.75 by 10 min.

The dose–response relationships for T1 and TOF were calculated for each 1 min after administration of the antagonist (figs 3, 4). The slopes of the lines describing T1 and TOF recovery after edrophonium were not significantly different from the corresponding lines after neostigmine. The lines did not deviate from parallelism, but those constructed at 10 min were shifted significantly to the left compared with those constructed at 5 min ($P < 0.001$) for both antagonists. The calculated ED values for T1 height and TOF ratio from 4 min onward for edrophonium and neostigmine are presented in figures 5 and 6, respectively. Some of the calculated ED values are not reported because they were outside the range of doses tested.

The potency ratios, or the potency of neostigmine expressed as a multiple of that of edrophonium are presented in table II. For the train-of-four ED_{50} values, the potency ratio did not change with time. In contrast, the potency ratio for the first twitch decreased significantly at 10 min (table II).

DISCUSSION

This study demonstrated that the dose–response relationships of edrophonium and neostigmine antagonism of mivacurium neuromuscular block were parallel and that, in the absence of antagonist, spontaneous recovery (after return to 10% first twitch height) to a TOF ratio of 0.75 occurred in 15.4 (12.7–18.1) min.

The short duration of action of mivacurium is

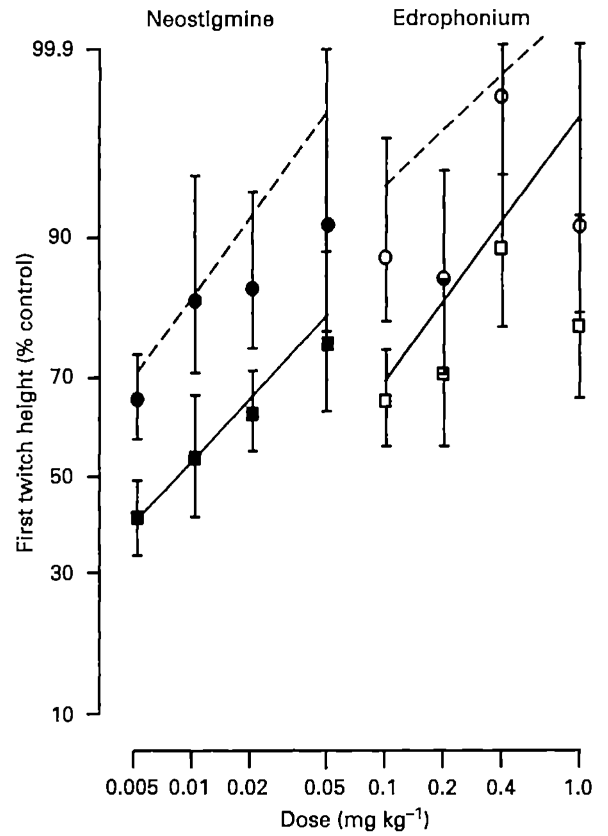

FIG. 3. Log dose–response relationships of first twitch recovery (% control) obtained 5 min (——) after administration of neostigmine (■) or edrophonium (□) and 10 min (—) after administration of neostigmine (●) or edrophonium (○). Individual points represent mean T1 attained with each dose and the bars represent 95 % confidence intervals.

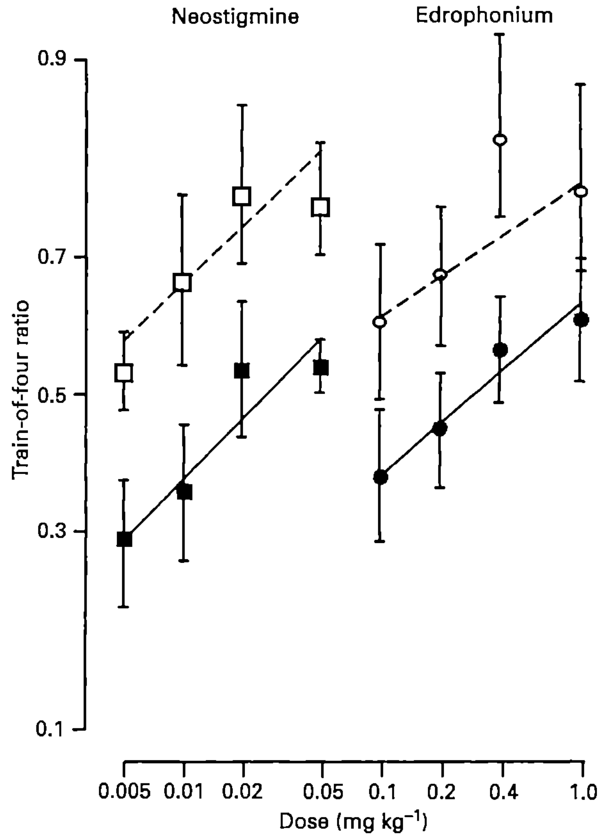

FIG. 4. Log dose–response relationships of train-of-four recovery obtained 5 min (——) after administration of neostigmine (■) or edrophonium (●) and 10 min (—) after administration of neostigmine (□) or edrophonium (○). Individual points represent mean TOF ratio attained with each dose and the bars represent 95 % confidence intervals.

related primarily to its hydrolysis by butyrylcholinesterase. A finding of particular interest was that both human butyrylcholinesterase and neostigmine were equally effective in antagonizing mivacurium in cats when antagonism was attempted at 90 % block of twitch height [13]. However, in the presence of 100 % twitch inhibition, Bownes and colleagues found that enzymatic antagonism through increased metabolism was more effective than antagonism by neostigmine [13]. Therefore, enzymatic antagonism would eliminate the concern regarding the antagonistic effect of neostigmine on metabolism of mivacurium [2]. Our results demonstrate that 25–75 %, 10–95 % recovery times of T1 and times to attain a TOF ratio of 0.75 were shorter ($P < 0.01$) following neostigmine- or edrophonium-induced recovery compared with spontaneous recovery (table I). Spontaneous recovery from 90 % mivacurium block to 95 % twitch height and TOF ratio of 0.75 occurred within 15 min (table I) and the average saving in time as a result of use of an antagonist was 7–9 min. Similar observations have been reported by others [2, 14]. Curran and colleagues [14] reported that, during nitrous oxide–oxygen–opioid anaesthesia, 25–75 % recovery time of T1 was shorter after neostigmine 0.06 mg kg^{-1} (mean 3 (SEM 0.2) min) compared with spontaneous recovery (6.5 (0.3) min).

Our data indicate that the potency ratio was not the same for single twitch and TOF. When reversal was attempted at 10 % T1 recovery from mivacurium block, 5.4 times as much edrophonium as neostigmine was required to achieve 50 % T1, but 11.39 times as much was needed to achieve a TOF ratio of 0.5 (table II). In this respect, our results are consistent with those of other investigators [15–17] who reported similar observations with other nondepolarizing neuromuscular blocking agents. It should be noted, however, that the increased dose requirements for both neostigmine and edrophonium to attain 70 % recovery of T1 height was proportionate, since the neostigmine: edrophonium potency ratios were similar (table II).

Donati and colleagues noted that, 10 min after injection of antagonist (after return to 10 % first twitch height) the neostigmine: edrophonium potency ratio for T1 was approximately 20 for both atracurium and vecuronium [17], 12 for pancuronium and 16 for tubocurarine [15]. This is in contrast with a corresponding potency ratio of 1.4 observed in our study (table II). We noted that the potency ratio either decreased significantly after administration of the antagonist (as for T1) or did not change at all, as noted with the TOF response. This observation is at variance with other reports [15–17] and our own observations with rocuronium [18] and pipecuronium [unpublished data]. We interpret these observations jointly as suggesting

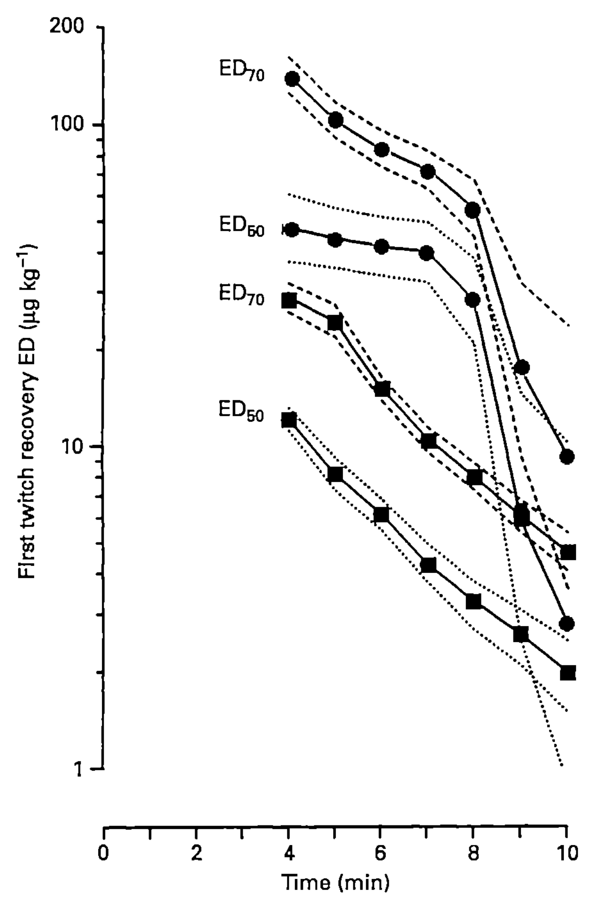

FIG. 5. Effective doses (ED) for 50% and 70% recovery (ED_{50} and ED_{70}) of first twitch height for neostigmine (■) and edrophonium (●). Broken lines indicate 95% confidence intervals.

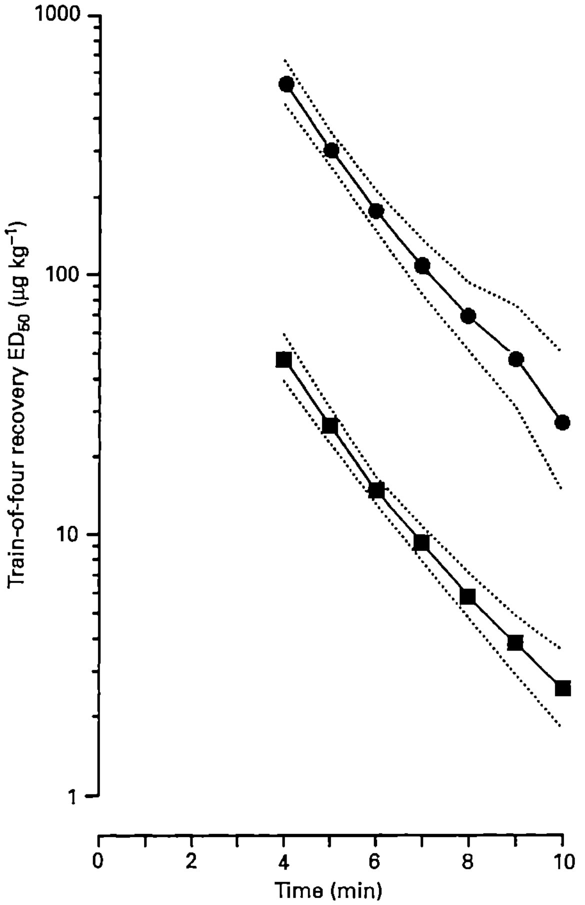

FIG. 6. Effective doses for 50% recovery (ED_{50}) of train-of-four ratio for neostigmine (■) and edrophonium (●). Broken lines indicate 95% confidence intervals.

that neostigmine inhibition of mivacurium metabolism [5] was manifested by the increase in potency of edrophonium over time. This confirms that the neostigmine:edrophonium potency ratio varies depending on the agent used, depth of block and end-point chosen.

The introduction of mivacurium into anaesthetic practice allows provision of clinical relaxation for periods of 15 min to 3 h or more. When mivacurium is administered to provide paralysis for surgical procedures of short (15–20 min) duration, to wait an additional 9 min, on average, for adequate spontaneous recovery to occur would represent an approximately 50% prolongation of the surgical time. If mivacurium infusions were to be used for longer surgical procedures, then allowing spontaneous recovery to occur could be advantageous.

In summary, the results of this study demonstrate that spontaneous recovery from 90% mivacurium block to 95% twitch height and TOF ratio of 0.75 occurred within 15 min. It also emphasizes that both neostigmine and edrophonium are able to produce

TABLE II. *Potency in relation to doses required for 50% (ED_{50}) and 70% (ED_{70}) recovery of first twitch height and for 50% (ED_{50}) train-of-four recovery, 5 and 10 min after injection of antagonist (mean (95% confidence intervals))*

	5 min	10 min	*P*
First twitch recovery			
ED_{50}			
Edrophonium (μg kg^{-1})	44.3 (35.8–54.8)	2.8 (0.75–10.2)	< 0.0001
Neostigmine (μg kg^{-1})	8.2 (7.3–9.2)	2.0 (1.5–2.5)	0.0001
Potency ratio	5.4 (3.9–6.8)	1.4 (0.4–2.4)	0.01
ED_{70}			
Edrophonium (μg kg^{-1})	103 (90.9–117)	9.2 (3.6–23.6)	< 0.0001
Neostigmine (μg kg^{-1})	24.6 (21.9–27.6)	4.7 (4.1–5.4)	< 0.0001
Potency ratio	4.18 (3.8–4.5)	1.95 (0.9–2.9)	0.0003
Train-of-four recovery			
ED_{50}			
Edrophonium (μg kg^{-1})	302 (260–352)	26.9 (14.6–49.6)	< 0.0001
Neostigmine (μg kg^{-1})	26.5 (22.6–31)	2.57 (1.8–3.6)	0.0001
Potency ratio	11.39 (10.5–12.3)	10.4 (0.7–20)	ns

dose-dependent antagonism of mivacurium-induced block. The dose–response curves for edrophonium and neostigmine were parallel. The potency ratio is not the same for single twitch and train-of-four responses. Edrophonium was less capable of antagonizing fade (potency ratio of 11.39–10.4) than first twitch (potency ratio of 1.1–5.4).

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COMPARISON OF PROPOFOL WITH THIOPENTONE FOR TREATMENT OF BUPIVACAINE-INDUCED SEIZURES IN RATS

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SUMMARY

Thirty Sprague–Dawley rats were paralysed with pancuronium and their lungs ventilated mechanically with 70% nitrous oxide and 0.5% halothane in oxygen. Bupivacaine 2 mg kg^{-1} min^{-1} was infused continuously i.v. until the animals died. At the onset of seizures, animals were given an i.v. bolus of propofol 1 mg kg^{-1} (n = 10), thiopentone 2 mg kg^{-1} (n = 10) or lipid vehicle (n = 10). Administration of propofol or thiopentone was repeated each time seizures restarted and lipid vehicle administrations were repeated at 2-min intervals until the electroencephalogram became isoelectric. All animals developed seizures, arrhythmias, isoelectric EEG and asystole. Administration of lipid vehicle induced no obvious changes in ongoing epileptiform activity. The initial doses of thiopentone and of propofol stopped epileptiform activity in all animals, usually within 6 s after administration. The seizure-free period after the initial administration of thiopentone and of propofol lasted, on average, 0.98 min and 1.72 min, respectively. We conclude that propofol may have value in treating seizures induced by bupivacaine. (Br. J. Anaesth. 1993; **71**: 715–719)

KEY WORDS

Anaesthetics, local: bupivacaine. Toxicity: convulsions. Brain: seizure threshold. Anaesthetics, intravenous: thiopentone, propofol.

Thiobarbiturates, particularly thiopentone, are effective in stopping local anaesthetic-induced seizures [1]. The increasing use of propofol for sedation and induction and maintenance of anaesthesia increases the likelihood that it may be available when a patient suffers a local anaesthetic-induced seizure. Propofol has anticonvulsant activity [2–4] but, to our knowledge, its effectiveness in stopping local anaesthetic-induced seizures has not been studied.

The objectives of this study were to determine if propofol terminated bupivacaine-induced seizures in lightly anaesthetized rats and to compare its efficacy with that of thiopentone.

METHODS

After obtaining approval by the Institutional Animal Care and Use Committee of Texas Tech University Health Sciences Center, we studied 30 Sprague–Dawley rats (222–326 g). Anaesthesia was induced with 2% halothane in oxygen in a 1-litre container. Halothane was administered by mask while the trachea was cannulated via a tracheostomy. The lungs were ventilated using a rodent ventilator (Harvard Apparatus, South Natick, Massachusetts), with a tidal volume of 10 ml kg^{-1} at a frequency of 50 b.p.m. Needle electrodes were placed for recording leads I, II, and modified V_1 of the electrocardiogram (ECG) and fronto-occipital electroencephalogram (EEG). Anaesthesia was maintained with 1–1.5% inspired halothane in oxygen while a cannula was placed in each femoral artery for blood sampling and arterial pressure (AP) measurements. A cannula was placed via a femoral vein into the vena cava and advanced to the level of the diaphragm for infusion of bupivacaine and another was placed in the opposite femoral vein for administration of other drugs (see below). ECG, EEG and AP were monitored on a chart recorder (Grass Medical Instruments, Quincy, Massachusetts). Mean AP (MAP) was calculated from the formula $\text{MAP} = \text{DAP} + (\text{SAP} - \text{DAP})/3$ (DAP = diastolic and SAP = systolic AP).

After surgery was completed, pancuronium 1.0 mg kg^{-1} was given i.v. to induce muscle paralysis and anaesthesia was changed to 0.5% halothane and 70% nitrous oxide in oxygen at least 30 min before the start of i.v. infusion of bupivacaine 2 mg kg^{-1} min^{-1}. Arterial blood-gas tensions were measured about 10 min before the start of the infusion and ventilation adjusted to achieve Pa_{CO_2} approximately 4.6 kPa. Blood-gas measurement was repeated after 5 min if ventilation was adjusted (0.3 ml per sample; never more than two samples).

At the onset of seizures, thiopentone 2 mg kg^{-1}, propofol 1 mg kg^{-1} or propofol vehicle 1 ml kg^{-1} (Liposyl II 10% Abbott Laboratories, North Chicago, IL) was injected rapidly i.v. A 0.2% thiopentone solution was prepared using saline as diluent, and a 0.1% solution of propofol was

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TABLE I. *Baseline data (mean (SD))*

	Weight (g)	pH	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)	HCO_3^- (mmol litre^{-1})	BE (mmol litre^{-1})	MAP (mm Hg)	HR (beat min^{-1})
Liposyl	241.5 (19.3)	7.38 (0.05)	4.8 (0.6)	15.4 (2.1)	22.3 (3.1)	−1.28 (3.4)	93 (18)	416 (43)
Propofol	270.1 (31.0)	7.42 (0.03)	4.4 (0.7)	14.9 (1.8)	21.9 (3.3)	−1.07 (3.1)	83 (12)	381 (40)
Thiopentone	233.5 (28.8)	7.38 (0.04)	5.1 (1.0)	15.1 (2.0)	22.5 (2.9)	−1.52 (2.3)	86 (25)	397 (64)

prepared using Liposyl as diluent. Bupivacaine infusion was continued and propofol or thiopentone was administered each time epileptiform activity appeared on the EEG. Epileptiform activity was defined as large amplitude (> 100 µV) repetitive sharp waves or spikes accompanied by facial twitching in animals with incomplete neuromuscular block. In the Liposyl group, lipid vehicle was injected at 2-min intervals. Arterial blood samples (1 ml) for measurement of bupivacaine concentrations were obtained before the start of bupivacaine infusion and at 2.5-min intervals until the animal died. Blood was replaced with an equal volume of isotonic saline. Doses of bupivacaine producing the following toxic end-points were determined: arrhythmia (cardiac rhythm disturbance accompanied by an abnormal pulsation on the AP trace); seizures (appearance of epileptiform activity on the EEG); isoelectric EEG (flattening of the EEG trace); asystole (the last recognized beat on the ECG, allowing 1 min for additional beats to appear).

Bupivacaine concentrations in plasma were measured by HPLC with ultraviolet detection [5] (lower limit detection 0.5 µg ml^{-1}; coefficient of variation (5 µg ml^{-1}) was < 3 %).

Statistical analysis

One-way analysis of variance (ANOVA) and the Student–Newman–Keuls test were used to compare differences between groups for plasma concentrations and threshold doses of bupivacaine, baseline values for mean arterial pressure, heart rate and arterial blood-gas tensions, and differences within groups for threshold doses of bupivacaine. Chi-square proportional analysis was used to test for significant differences between groups with respect to occurrence of arrhythmias before seizures and asystole *vs* ventricular beats as the terminal ECG pattern. Multiple analysis of variance (MANOVA) and Exact *F* test statistics were used to compare HR and MAP *vs* time for the three treatment groups. Probit analysis was used to analyse cumulative number of animals with asystole or with sinus arrest *vs* bupivacaine dose. Statistical significance was accepted at $P \leqslant 0.05$.

RESULTS

MAP, HR and blood-gas values before infusion of bupivacaine were similar for the treatment groups (table I).

Toxic endpoints. All animals developed seizures, arrhythmias, isoelectric EEG and asystole. Seizures occurred first, with the exception of five animals which experienced arrhythmias before seizure (two in the Liposyl group, two in the thiopentone group and one in the propofol group).

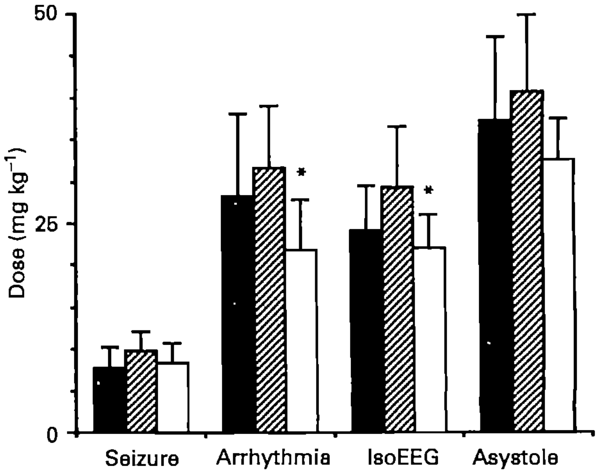

FIG. 1. Doses of bupivacaine producing the various toxic endpoints. Data from animals that developed arrhythmias before seizures were excluded from the arrhythmias calculation. *Propofol (■) significantly different ($P < 0.05$) from thiopentone (□). ■ = Lipid vehicle.

The doses of bupivacaine that induced the first seizure were similar for all three treatment groups (fig. 1). Because therapeutic intervention began as soon as seizures started, this toxic endpoint was the only one that occurred before administration of Liposyl, thiopentone or propofol (with the exception of arrhythmias in the five animals that had arrhythmias before seizures). The other toxic endpoints, therefore, were subject to treatment influences.

Doses of bupivacaine that induced arrhythmias, isoelectric EEG and asystole were greater in the propofol treatment group compared with the other treatment groups (data from the five animals that had arrhythmias before seizures were not included in this comparison because treatment was instituted after the arrhythmias). Doses of bupivacaine that induced arrhythmias and isoelectric EEG were significantly smaller in the thiopentone group compared with the propofol group (fig. 1).

While doses of bupivacaine that produced arrhythmias and isoelectric EEG were not significantly different within treatment groups, the order in which arrhythmias and isoelectric EEG developed was significantly different in the thiopentone group. Arrhythmias occurred first more often (five of eight animals) in the thiopentone group than in the lipid vehicle (one of eight) and propofol groups (three of nine).

Anticonvulsant effect. Liposyl injections induced

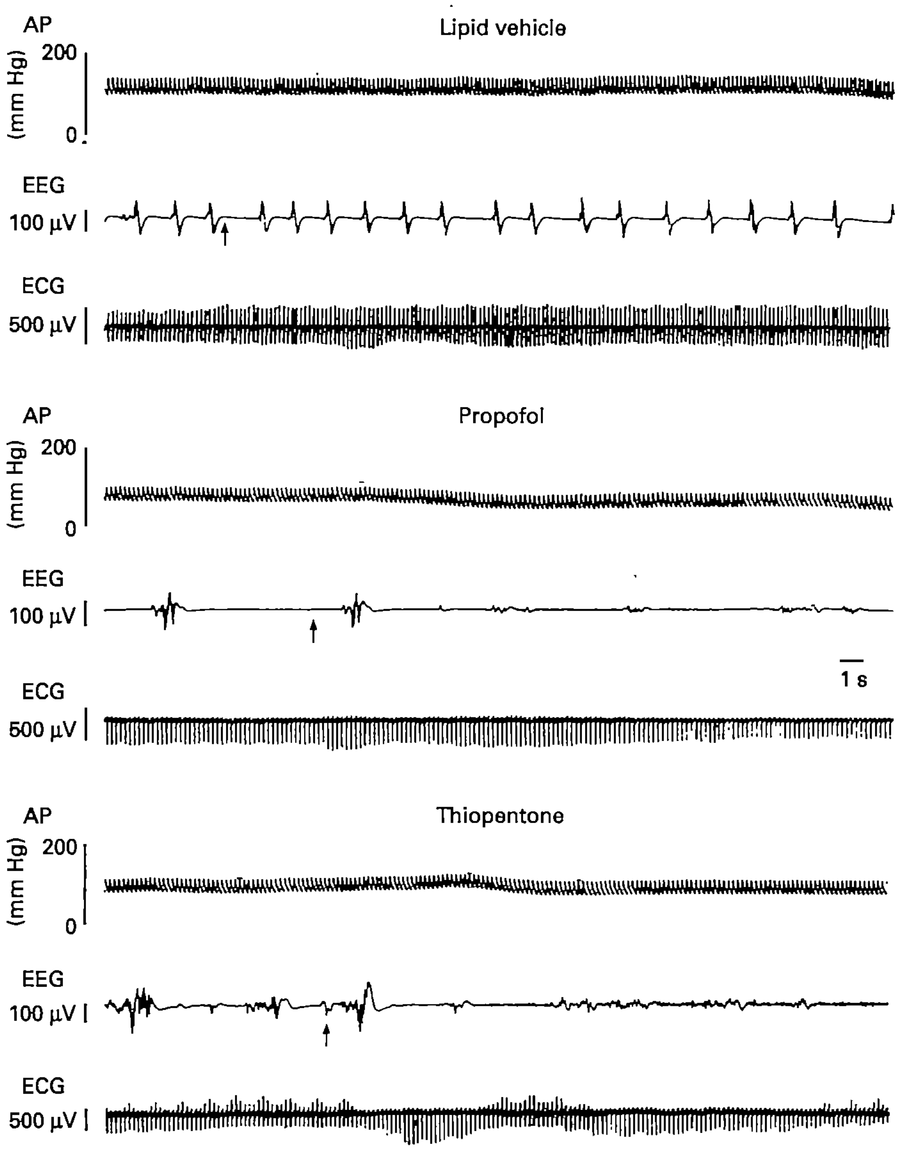

FIG. 2. Arterial pressure (AP), EEG and Lead II ECG recordings, illustrating changes induced by the initial injection (arrow) of lipid vehicle, propofol or thiopentone.

no obvious changes in ongoing epileptiform activity. The initial doses of thiopentone and of propofol stopped epileptiform activity in all animals (fig. 2), usually within 6 s. The mean (SD) seizure-free periods after the initial injection of thiopentone and of propofol were 0.98 (0.6) min and 1.72 (1.25) min, respectively (ns). Repeat injections of thiopentone or propofol stopped seizures (except for the third and fourth injections of propofol in one rat which received four injections). The number of times seizures appeared and thiopentone (4.6 (1.7) times) or propofol (6.6 (3.9) times) was administered varied in each group, as did the duration of seizure-free periods. However, the differences between groups were not significant.

Cardiovascular changes. As bupivacaine dose increased, HR decreased, as did MAP after an initial small increase (significant changes over time). The rate of HR change was greater in the thiopentone group compared with the two other groups, but not significantly so. However, MAP decreased significantly faster in the thiopentone group compared with the propofol and lipid vehicle groups (fig. 3). Lipid vehicle injections every 2 min had no effect on arterial pressure. Thiopentone injections usually induced a slight increase in MAP, followed by a transient decrease; propofol induced a transient decrease in MAP. There was no significant difference in MAP decrease induced by the initial injection of propofol or thiopentone (fig. 4).

The terminal ECG pattern preceding asystole was either sinus or ventricular beats. The terminal ECG pattern was ventricular in seven of 10 animals in the thiopentone group, five of 10 animals given propofol and four of 10 given Liposyl (table II). Doses of bupivacaine producing sinus arrest were significantly smaller in the thiopentone group compared with the propofol group. The doses producing this effect in the Liposyl group did not differ significantly from the doses of bupivacaine producing sinus arrest in the two other groups.

Drug concentrations. Plasma concentrations of bupivacaine in the three treatment groups were similar (fig. 5).

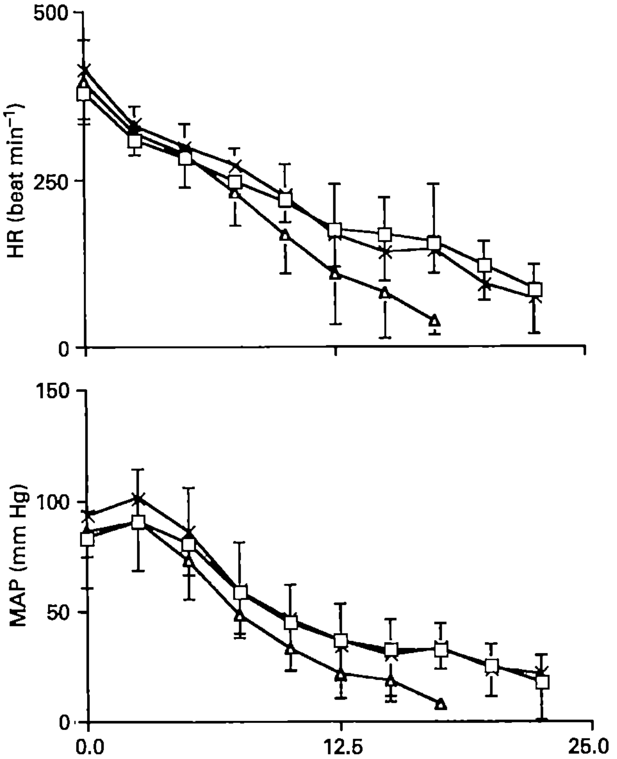

FIG. 3. HR *vs* bupivacaine infusion time (upper graph) and MAP *vs* bupivacaine infusion time (lower graph). $n = 10$ until 10 min for lipid vehicle (×) and thiopentone (△), and until 12.5 min for propofol (□), then progressively fewer as animals died.

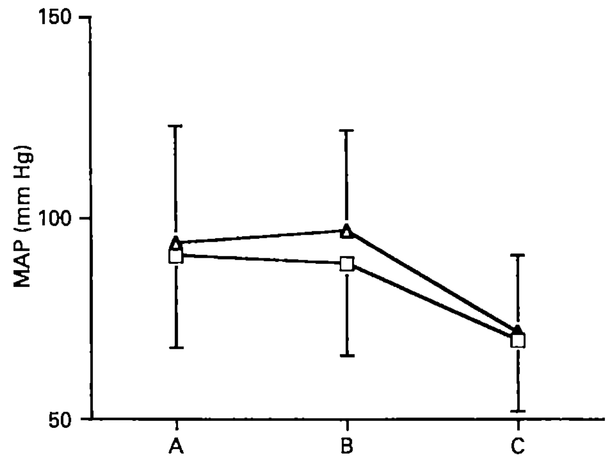

FIG. 4. Changes in MAP induced by initial doses of thiopentone (△) and propofol (□). A = Just before propofol or thiopentone injection; B = greatest pressure after injection; C = smallest pressure after injection.

TABLE II. *Terminal ECG pattern preceding asystole*

	Sinus arrest	Ventricular beats	Other
Liposyl	6	4	—
Propofol	5	5	—
Thiopentone	2	7	1

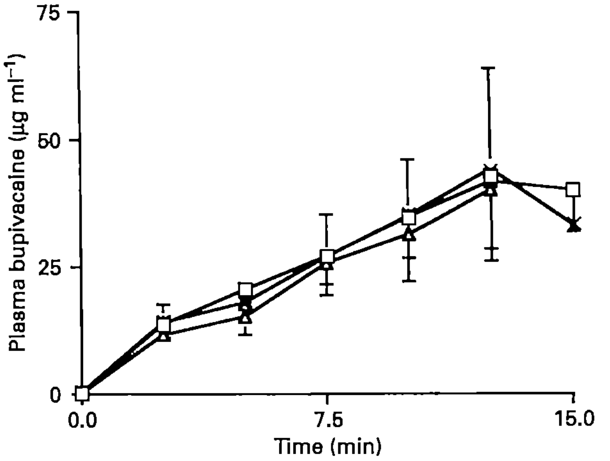

FIG. 5. Bupivacaine plasma concentration *vs* infusion time for the lipid vehicle (×), propofol (□) and thiopentone (△) groups. $n = 7$–10 until 12.5 min and $n = 3$–5 for 15 min. Data beyond 15 min not plotted because of small number.

DISCUSSION

In this study, the anticonvulsant actions of propofol and thiopentone were similar, even though the dose of propofol (1 mg kg^{-1}) was 50 % that of thiopentone (2 mg kg^{-1}); the relative potency of propofol and thiopentone for this effect is thus similar to their relative hypnotic potency [6]. Similar effects of these two drugs may be expected because it is thought that propofol, in common with the barbiturates, exerts its anticonvulsant, sedative, hypnotic and anaesthetic effects, at least in part, by enhancing GABA-mediated chloride ion conductance in some neuronal systems [7].

The short duration of anticonvulsant action of thiopentone and propofol is not surprising, given their pharmacokinetic characteristics—rapid redistribution [8], and the fact that bupivacaine infusion was continued at a relatively rapid rate after thiopentone or propofol was injected. In mice, the sleeping time induced by propofol 5 mg kg^{-1} i.v. is about 3 min [9].

There is some evidence that propofol may be preferable to thiopentone for treatment of bupivacaine-induced seizures; for example, the cumulative percentage asystole *vs* bupivacaine dose and cumulative percentage sinus arrest *vs* bupivacaine dose curves for the thiopentone group were to the left of those for the lipid vehicle and propofol groups. Also, the doses of bupivacaine that induced arrhythmias and isoelectric EEG were significantly smaller in the thiopentone group compared with the propofol group.

The effects of propofol and thiopentone on the heart are qualitatively, but not quantitatively, similar. For instance, both depress myocardial contractility, but for an equivalent anaesthetic effect, propofol depresses myocardial contractility less than thiopentone [10, 11].

Propofol increases coronary blood flow markedly; thiopentone does not [12]. It is interesting that intracoronary injection of bupivacaine decreases coronary blood flow [13]. The decrease is accompanied by, and presumably caused by, a decrease in myocardial oxygen consumption. Positive and negative benefits might be produced if propofol antagonizes the effects of bupivacaine on coronary blood flow. A beneficial effect might include increased oxygen and nutrient delivery and increased washout of bupivacaine and metabolic wastes (e.g. lactate, and carbon dioxide). A detrimental consequence of increased coronary flow would be increased delivery of bupivacaine to the heart, especially under the conditions of this study, in which bupivacaine was infused continuously.

Light anaesthesia with halothane and nitrous oxide and the use of pancuronium to maintain muscle paralysis may modify toxic responses to bupivacaine. Nevertheless, we conclude that propofol is effective in stopping bupivacaine-induced seizures. Further studies are required to determine if outcomes are better when propofol is used instead of thiopentone. Also, studies comparing propofol and benzodiazepines are required, as one authoritative text indicates that diazepam is the drug of choice for treating local anaesthetic-induced seizures [14].

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PULMONARY VASCULAR EFFECTS OF TRINITROGLYCERIN AND ISOSORBIDE DINITRATE AFTER CARDIOPULMONARY BYPASS[†]

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AND J. HEINONEN

SUMMARY

We have compared the systemic and right ventricular haemodynamic effects of trinitroglycerin (TNG) and isosorbide dinitrate (ISDN) in patients recovering from coronary artery bypass grafting. Each of the 16 patients was given increasing i.v. doses of the two nitrates in a random order and double blind fashion until the target of a 25% decrease in mean pulmonary artery pressure (MPAP) was achieved. Total doses of TNG 9 (6–12) μg kg^{-1} (mean, 95% confidence interval) and ISDN 148 (76–220) μg kg^{-1} were given during infusions of 22 (18–25) min and 34 (28–41) min duration, respectively. The target decrease in MPAP was produced with infusion rates of TNG 0.5 (0.4–0.7) μg kg^{-1} min^{-1} and ISDN 5.8 (4.1–7.5) μg kg^{-1} min^{-1}. These doses produced similar acute decreases in MPAP and similar effects on pulmonary and systemic vascular resistances and systemic and right ventricular haemodynamic variables. We conclude that TNG is more than 10 times as potent as ISDN in its acute haemodynamic effects in cardiac surgical patients in the immediate postoperative period. Both nitrates have relatively greater effect on the pulmonary than the systemic vasculature. (Br. J. Anaesth. 1993; **71**: 720–724)

KEY WORDS

Lung: vascular resistance. Heart: trinitroglycerin, isosorbide dinitrate.

I.v. organic nitrates are effective in reducing pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) [1]. In addition to the pulmonary vascular effects, nitrates also have effects on systemic haemodynamic state. However, in some clinical situations a drug with more selective effects on the pulmonary vasculature would be desirable. A typical case would be a patient recovering from cardiopulmonary bypass (CPB) with signs of right ventricular failure resulting from increased PVR but without systemic hypertension [2, 3]. Even after uncomplicated heart operations, the pulmonary vasculature may be sensitized to vasoconstrictors [4–6] and the right ventricle may be especially vulnerable to increased afterload [2, 3, 6].

Trinitroglycerin (TNG) is the most commonly used i.v. organic nitrate in cardiac surgical patients. The pulmonary vascular effects of TNG are accompanied generally by systemic haemodynamic effects [1]. Another nitrate, isosorbide dinitrate (ISDN), when given as a small i.v. bolus dose after CPB, was found to decrease PAP and PVR without significant systemic haemodynamic effects [7]. This finding raised the possibility that ISDN might be more selective in its effect on pulmonary vasculature than TNG. In the present study, we have compared the pulmonary and systemic vascular effects of i.v. TNG and ISDN in patients recovering from coronary artery bypass grafting (CABG).

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and informed consent was obtained. We studied 25 patients in the recovery room after elective CABG. All had a preoperative left ventricular ejection fraction $\geqslant 0.35$. Patients not in sinus rhythm and those requiring artificial pacemaker or with signs of postoperative myocardial ischaemia requiring medication with nitrates had been excluded. In addition, four patients with technical problems in the measurement of right ventricular ejection fraction (RVEF) and five patients who developed a low output state (cardiac index < 2.0 litre min^{-1} m^{-2}) requiring therapy with additional fluids or inotropic drugs were excluded. Thus 16 patients completed the study. They were allocated randomly to receive TNG and ISDN in a cross-over, double-blind fashion: eight received TNG as the first drug and eight were given ISDN first. The characteristics of these patients are given in table I.

Anaesthesia and cardiopulmonary bypass

The patients received their regular oral medication (long-acting nitrates, calcium channel blockers and beta-adrenergic blockers) until and including the

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TABLE I. *Characteristics of the 16 study patients (mean (range or 95% confidence interval) or number of patients)*

Age (yr)	57 (range 44–73)
Weight (kg)	76 (70–82)
Height (cm)	171 (165–176)
Ejection fraction of left ventricle (%)	54 (47–60)
Medication	
Beta-adrenergic blocker	13
Calcium channel blocker	11
Nitrate	15
Aortic cross-clamp time (min)	44 (36–52)
Cardiopulmonary bypass time (min)	93 (80–107)
Number of distal grafts	3.8 (range 2–6)
Right coronary artery bypassed	13

morning of surgery. They were premedicated with hyoscine 6 µg kg^{-1} and morphine 200 µg kg^{-1} i.m. Anaesthesia was induced with fentanyl 30 µg kg^{-1} and diazepam 0.1 mg kg^{-1} and maintained with an infusion of fentanyl 0.3 µg kg^{-1} min^{-1} until the start of CPB, when the rate was reduced to 0.15 µg kg^{-1} min^{-1}, continued until the end of surgery. Anaesthesia was supplemented with enflurane or halothane and neuromuscular block was produced with pancuronium. After tracheal intubation, the patient's lungs were ventilated mechanically with a mixture of oxygen and air ($F\text{I}_{O_2}$ 0.5) and the minute volume was adjusted to maintain normocapnia as monitored by end-tidal carbon dioxide concentration and intermittent blood-gas analyses. During CPB the airways were disconnected from the ventilator and vented to ambient air.

For CPB, non-pulsatile pump flow, membrane oxygenation, moderate hypothermia and isovolaemic haemodilution were used. Myocardial protection during aortic cross-clamping was achieved with external cooling of the heart and with cold, crystalloid potassium cardioplegia solution (Plegisol, Abbot, North Chicago, U.S.A.) given antegradely and intermittently. Systemic anticoagulation for CPB was produced with heparin and reversed with protamine sulphate according to the values of blood activated clotting time.

Study design

The study was started in the recovery room within 2 h of CPB. Continuous infusions of fentanyl 0.1 µg kg^{-1} min^{-1} and pancuronium 0.5 µg kg^{-1} min^{-1} were given. Patients' lungs were ventilated mechanically (IMV-Bird, Bird Products Corporation, Palm Springs, U.S.A.) with a mixture of oxygen and air ($F\text{I}_{O_2}$ 0.5) with a positive end-expiratory pressure of 6 cm H_2O. Normocapnia was maintained by monitoring end-tidal carbon dioxide concentration and by performing blood-gas analyses before and at the end of each period of test drug administration. Systemic arterial pressure was measured via an indwelling cannula in the radial artery. A modified pulmonary artery catheter with a rapid response thermistor (Swan–Ganz Thermodilution Ejection Fraction/Volumetric Catheter, American Edwards Laboratories, Santa Ana, U.S.A.) and an accompanying computer (REF-1 Ejection Fraction/Cardiac Output Computer, American Edwards Laboratories, Santa Ana, U.S.A.) were used to measure pulmonary artery pressures, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO) and right ventricular ejection fraction (RVEF), and to calculate right ventricular end-diastolic volume (RVEDV) and right ventricular end-systolic volume (RVESV). All intravascular pressures and ECG leads II and V5 were recorded continuously (PCWP was measured intermittently) and CO and RVEF were measured before and at the end of each test drug administration. Mean arterial pressure (MAP), MPAP, cardiac index (CI), systemic (SVR) and pulmonary (PVR) vascular resistances and left (LVSWI) and right (RVSWI) ventricular stroke work indices were calculated using standard formulae. For the determination of intravascular pressures, the end-expiratory pressure waveforms were used. Blood samples were obtained from the radial and pulmonary arteries simultaneously for measurement of blood-gas tensions, oxyhaemoglobin saturation and blood haemoglobin content. These values enabled calculation of intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$) [8].

Administration of the test drug was started when the haemodynamic state of the patient was stable in the recovery room. After baseline measurements, patients received TNG and ISDN in random order with a washout period of at least 30 min between drug infusions. TNG and ISDN were dissolved in isotonic saline to produce concentrations of 0.25 mg ml^{-1} and 1 mg ml^{-1}, respectively, and the drugs were given using an infusion pump. The drug infusion was started at a dose of 4 ml h^{-1} and increased every 4 min in increments of 4 ml h^{-1}: TNG started at a rate of 1 mg h^{-1} and the infusion rate was increased by increments of 1 mg h^{-1} and ISDN started at a rate of 4 mg h^{-1} and increased by increments of 4 mg h^{-1}. Each drug was given until a 25% decrease in MPAP had occurred. Thereafter, the infusion rate was maintained unchanged for at least 5 min. If no further decrease in MPAP was observed, measurements were taken and the drug infusion discontinued. After the haemodynamic changes had returned to a stable baseline, the other test drug was given in a similar fashion.

Statistical analyses

To compare the effects of the two drugs, data were analysed using the two-sample *t* test as described by Armitage and Berry [9] for crossover trials. We tested for treatment effect (is there any difference in the effects of the two test drugs?), period effect (does it matter if the test drug is given as the first or the second drug?) and for any interaction between the treatment and period effects. To evaluate the effect of each test drug *per se* (within-treatment effect), the conventional paired *t* test was applied for the haemodynamic variables. The results are presented as the mean (95% confidence intervals).

RESULTS

Conditions before the administration of TNG and ISDN were not significantly different (table II). The washout period between drug administrations was 45 (42–48) min.

TABLE II. *Haemodynamic effects of TNG and ISDN (mean (95% confidence interval)); 16 treatments with both drugs.* $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ *compared with value before drug*

	TNG		ISDN	
	Before	During	Before	During
HR (beat min^{-1})	93 (86–100)	93 (87–100)	91 (86–97)	93 (86–100)
CI (litre min^{-1} m^{-2})	2.8 (2.6–3.0)	2.9 (2.6–3.2)	2.8 (2.5–3.0)	2.8 (2.5–3.1)
MAP (mm Hg)	85 (80–91)	75 (67–82)***	85 (81–90)	75 (68–82)***
MPAP (mm Hg)	20.3 (18.9–21.8)	14.9 (13.9–16.0)***	20.1 (19.1–21.1)	14.9 (14.0–15.8)***
CVP (mm Hg)	9.3 (8.0–10.5)	7.4 (6.2–8.7)***	8.9 (8.0–9.9)	6.8 (5.7–7.9)***
PCWP (mm Hg)	10.5 (9.2–11.8)	8.3 (7.3–9.3)***	10.1 (9.0–11.3)	7.9 (6.9–8.9)***
RVEDP (mm Hg)	10.1 (9.0–11.1)	8.6 (7.5–9.6)***	10.1 (9.0–11.2)	8.0 (7.1–8.9)***
RVEF (%)	40.8 (38.3–43.3)	43.6 (40.1–47.0)	41.7 (37.7–45.6)	44.3 (40.8–47.7)
RVEDV (ml)	141 (126–156)	135 (121–150)	141 (123–158)	131 (117–145)*
RVESV (ml)	84 (74–94)	77 (67–87)	83 (70–96)	74 (64–83)*
SVR (dyn s cm^{-5})	1184 (1059–1309)	1024 (869–1178)***	1217 (1066–1367)	1062 (928–1197)**
PVR (dyn s cm^{-5})	156 (127–184)	104 (81–127)***	160 (132–188)	109 (94–124)***
RVSWI (g m m^{-2})	4.6 (3.9–5.2)	3.2 (2.6–3.8)***	4.7 (3.9–5.5)	3.4 (2.7–4.0)***
LVSWI (g m m^{-2})	31.1 (27.1–35.0)	28.4 (23.2–33.7)	31.4 (27.8–35.0)	28.1 (23.3–32.9)*
Qs/*Qt* (%)	15.0 (12.6–17.3)	17.9 (15.2–20.6)**	15.3 (12.6–18.0)	17.8 (14.8–20.8)**

The target of a 25% decrease in MPAP was reached within 22 (18–25) min with TNG and within 34 (28–41) min with ISDN. The goal was achieved with TNG 0.5 (0.4–0.7) μg kg^{-1} min^{-1} and with ISDN 5.8 (4.1–7.5) μg kg^{-1} min^{-1}. The total doses of TNG and ISDN administered were 9 (6–12) μg kg^{-1} and 148 (76–220) μg kg^{-1} and the mean doses (total dose/infusion time) were 0.4 (0.3–0.5) μg kg^{-1} min^{-1} and 3.8 (2.7–4.9) μg kg^{-1} min^{-1}, respectively.

The analyses revealed no significant differences between the effects of the two drugs (treatment effect), no period effect and no treatment–period interaction effect, which indicates that both test drugs had identical haemodynamic effects which were independent of the order of administration [9]. The changes in heart rate (HR) and CI with each drug were not significant (table II). Both drugs decreased MAP, MPAP, CVP, PCWP and right ventricular end-diastolic pressure (RVEDP) significantly. RVEF increased slightly with both drugs, but this change was not statistically significant. RVEDV and RVESV decreased with both drugs, but the changes were significant only with ISDN. SVR, PVR and RVSWI decreased significantly with both drugs, but LVSWI decreased significantly only with ISDN. *Qs*/*Qt* increased significantly with both drugs.

MPAP decreased 26 (25–28) % with TNG and 26 (24–28) % with ISDN, while PVR decreased 36 (28–45) % and 33 (24–41) %, respectively. MAP decreased 12 (6–19) % with TNG and 12 (7–18) % with ISDN, while SVR decreased 11 (6–17) % with TNG and 12 (6–17) % with ISDN. Thus both TNG and ISDN had a relatively greater effect on pulmonary than on systemic vasculature.

DISCUSSION

The main purpose of the present study was to compare the selectivity of ISDN and TNG on the pulmonary vasculature. When given in doses producing 25% decrease in MPAP, both nitrates had significant but equal systemic haemodynamic effects, indicating no difference in selectivity. The study confirmed, however, that i.v. nitrates generally have a more potent effect on the pulmonary than on the systemic vasculature, as assessed by relative changes in MPAP and MAP. This equality of haemodynamic effect of TNG and ISDN was obtained when the drugs were given in a total dose ratio of 1:16 or in a final infusion rate ratio of 1:11. The changes in calculated PVR and SVR also were similar with both nitrates, the decreases observed in PVR being more marked than those in SVR. This observation also seems to indicate that both nitrates have a more selective effect on pulmonary vasculature than on systemic vasculature. The ability of the calculated vascular resistances, PVR in particular, to reflect the vasodilatory effects of drugs has been questioned. Analysing pressure–flow relationships with varying pulmonary blood flow to extrapolate the critical closing pressure is a more correct way of assessing true resistance across the pulmonary vascular bed [10], but obtaining data for such analyses requires interventions which were not possible in our patients. However, it is of note that in our study the flow (cardiac output) remained unchanged, while MPAP and MAP decreased, after administration of the drugs. Therefore we consider that, even without knowledge of pressure–flow relationships in our patients, the decreases in the calculated resistances reflect vasodilatation [10].

The target of a 25% decrease in MPAP chosen for the present study was based on previous observations from this institution. We have found that MPAP is increased often by this amount after CPB [5, 6, 11]. An additional increase in MPAP of similar magnitude is induced by moderate hypercapnia during the postbypass period [4–6]. Patients in the present study were maintained at normocapnia and had only slightly increased PVR. In order to ensure stable study conditions, anaesthesia was maintained with a continuous infusion of fentanyl and shivering was prevented with an infusion of pancuronium. Thus data in this study were obtained under stable conditions. Our patients had good cardiac function and, therefore, our results may not be applicable directly to subjects in whom deterioration of RV function or more marked increases in PAP and PVR prevail.

The pulmonary vascular effects of TNG after CABG have been well documented. With average doses of 0.7–1.0 $\mu g\ kg^{-1}\ min^{-1}$, significant decreases in PAP [12, 13] and PVR [14] have been reported. These infusion rates have been accompanied also by significant systemic haemodynamic effects—decreases in MAP [12, 13] and SVR [13, 14]. Our findings with the mean dose of TNG 0.5 $\mu g\ kg^{-1}\ min^{-1}$ are in agreement with these previous results.

Using increasing infusion rates of ISDN, Gwilt, Petri and Reid [15] studied non-surgical patients with severe acute left ventricular failure. Although their pulmonary artery pressures at baseline were markedly greater than in our patients, the results in these two studies are very similar. Thus, with the dose of 400 $\mu g\ min^{-1}$ Gwilt, Petri and Reid found a 25 % decrease in MPAP (from 36 to 27 mm Hg), whereas we observed a similar decrease of 25 % with a dose of 434 $\mu g\ min^{-1}$. Furthermore, with this dose of ISDN Gwilt's group found decreases of 10 % in MAP (compared with 12 % in our study), 6 % in SVR (12 %) and 28 % in PVR (33 %). Both studies showed no significant changes in CI or HR. Parsons, Wetzel and Mohandas [7] administered a small bolus dose of ISDN 250–300 µg to normotensive patients after cardiac surgery. They found significant decreases in MPAP (13 %) and PVR (23 %), but no systemic haemodynamic effects. The responses were independent of the prevailing MPAP.

We found similar haemodynamic changes with TNG and ISDN. This is in accordance with the observations of Roth and colleagues [16], who used TNG or ISDN to decrease PCWP in patients with acute myocardial infarction. With doses of each drug that produced comparable reductions in PCWP, they observed similar pulmonary and systemic haemodynamic changes.

There are some data indicating that infusion of TNG may improve RV performance in patients undergoing CABG [17]. Temporary depression of RV function is not uncommon after cardiac surgery, and it seems to respond favourably to inotropes or vasodilators [18]. In our patients, the decrease in afterload of the RV (PVR) did not cause an increase in RVEF or CO with either nitrate. This may not be unexpected in patients with good RV function and without markedly increased PVR. In addition, the decrease in the preload of the RV may have counteracted the effect of the afterload reduction on RVEF, which remained unchanged.

In the present study, we have shown that TNG, on a weight basis, is more potent than ISDN in its haemodynamic effects. Depending on whether this assessment is based on the total dose administered during the whole infusion period or on the maximal infusion rate given at the target decrease in MPAP, TNG is 16 or 11 times as potent as ISDN. This calculation seems to agree with our recent observation that TNG is eight times as potent as ISDN in its venodilator activity and even more potent in its arteriolar dilator activity when given as bolus doses during hypothermic CPB [19]. Both our studies evaluated acute haemodynamic effects of nitrates in cardiac surgical patients. However, during infusions of longer duration, isosorbide mononitrates (the active metabolites of ISDN) may contribute to the effects observed during the administration of ISDN. Thus a different ratio may be obtained for equipotent doses of TNG and ISDN in such situations. In fact, Cintron and colleagues [20] found, at the end of a 24-h infusion of TNG or ISDN given to decrease an increased PCWP in patients with acute myocardial infarction, that the dose ratio for these drugs was 1:1.5.

The present study showed that i.v. TNG and ISDN decreased PVR rapidly when the infusion rate was increased with frequent increments. With such a scheme, TNG was clearly more potent than ISDN. A 25 % decrease in MPAP obtained by these drugs was associated also with smaller systemic haemodynamic changes. These changes were similar with TNG and ISDN.

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REVIEW ARTICLE

ACUTE EFFECTS OF OBSTRUCTIVE SLEEP APNOEA

R. J. O. DAVIES AND J. R. STRADLING

The pharyngeal airway narrows when pharyngeal muscle tone decreases. During sleep, partial collapse at this level leads to snoring, and complete collapse to obstructive sleep apnoea [25]. Such upper airway incompetence is relatively common: 17% of randomly selected normal British men snore [60]; one in 300 have severe obstructive sleep apnoea and cannot maintain a patent airway in any sleeping posture [60]. In hospital inpatient cohorts the prevalence is greater still. In one middle-aged group with ischaemic heart disease, significant obstructive sleep apnoea affected 14% of the sample [30].

Obstructive sleep apnoea has a range of undesirable acute effects which may be avoided by appropriate management. This review considers the causes of upper airway collapse, its consequences and treatment for the patient in hospital.

Aetiology of upper airway collapse during sleep

The patency of the muscular pharynx depends on the balance of forces acting across the pharyngeal wall. Muscle tone widens the airway, while external pressure from the peripharyngeal tissues, combined with intraluminal negative inspiratory pressures, narrow it. Any factor which adversely affects this balance tends to provoke airway collapse. Increased peripharyngeal soft tissue reduces sleeping airway calibre, probably through a simple mass effect [38]. In adults, neck fat deposition is the commonest factor predisposing to obstructive sleep apnoea; the circumference of the neck is a simple predictor of those at risk [13]. Internal airway narrowing as a result of retrognathia [49], adenotonsillar hypertrophy [61], craniofacial abnormalities [5, 33], nasal obstruction [29] and pharyngeal masses [66] also has a role. In children, large tonsils and adenoids are the usual reason for sleep apnoea, and among children awaiting tonsillectomy more than 50% have some respiratory disturbance during sleep [61]. Finally, a reduction in upper airway muscle tone caused by neuromuscular blocking drugs, sedatives [19, 44] and some antihypertensive drugs [41] exacerbates airway incompetence. This reduction in tone also underlies the widely recognized association between alcohol intake, snoring and obstructive sleep apnoea [31, 54, 63]. Similar effects have been shown for benzodiazepines [19, 44]. Neuromuscular diseases also may cause obstructive sleep apnoea through reductions in upper airway tone [20].

In hospital, several influences conspire to worsen any tendency to upper airway collapse. Hypnotic, analgesic and sedative drugs are often necessary, and are used to minimize sleep deprivation, which itself worsens sleep apnoea [24]. Patients may be obliged to sleep in a supine position because of the presence of i.v. and urinary catheters, monitors, and so on. This posture is the worst for those at risk of airway collapse, and about one in 50 men develop obstructive sleep apnoea in this position [60].

Identifying patients at risk of obstructive sleep apnoea

In adults, obstructive sleep apnoea should be suspected in those who snore and report daytime sleepiness [25]. There may also be a history of sleep apnoea witnessed by a partner [11]. Physical signs are less helpful. In adults who report snoring and sleepiness, a neck circumference greater than 43 cm (17 inches) suggests sleep apnoea is likely [13], and retrognathia or a small crowded pharynx supports the diagnosis. In children, sleepiness is combined with hyperactivity and antisocial behaviour [22], snoring is usual and large tonsils and adenoids are generally present [22].

When possible, suspected sleep apnoea should be documented with a sleep study before a hospital admission which may exacerbate the condition. However, for many patients this is not possible, and diagnosis is made only when the characteristic repetitive apnoeas are observed: the sleeping patient stops breathing (and making respiratory sounds), but continues to make respiratory efforts. The apnoea usually lasts for about 30 s, although pauses of up to 1 min may occur. At the end of this period, ventilation restarts suddenly as the pharynx reopens at arousal; often, but not always, this is associated with a loud snort and subsequent snoring. The ventilatory phase usually lasts about 15 s and is often associated with body movements.

The main clinical differential diagnosis to be made is with Cheyne–Stokes respiration resulting from unstable ventilatory control [36]. During typical Cheyne–Stokes respiration, the frustrated inspiratory efforts are absent, ventilation waxes and wanes smoothly, and the sound of pharyngeal opening at

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Complications: obstructive sleep apnoea. Sleep apnoea.

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the return of inspiration is absent. Arousal from sleep and movement are seen during the ventilatory phases of both abnormalities [15, 25, 27]. Although it is usually possible to decide which abnormality is responsible for the periodic breathing, this may be difficult. Some patients with apnoea initiated by upper airway collapse make minimal respiratory efforts during the apnoea [32]; secondary upper airway collapse is common during Cheyne–Stokes respiration [2]. In difficult subjects, a trial of nasal continuous positive airway pressure to ensure upper airway patency may be needed to resolve the issue.

Adverse effects of sleeping upper airway obstruction

The adverse effects of obstructive sleep apnoea may be classified into two groups: the apnoea–arousal–ventilation cycle has substantial effects on haemodynamics, autonomic tone and arterial blood-gas tensions; and sleep disruption and vascular instability cause long-term morbidity and mortality.

Acute effects of obstructive sleep apnoea

Subjects with severe obstructive sleep apnoea exhibit a repetitive apnoea–arousal cycle during all stages, and in all positions adopted during sleep. A typical night may include 300–400 such events. Each apnoea causes haemodynamic instability, hypoxaemia, mild hypercapnia and marked autonomic disturbance.

The haemodynamic changes are multifactorial. The frustrated inspiratory efforts of repeated apnoea decrease arterial pressure–pulsus paradoxus [43]. As the apnoea extends, increasing asphyxia makes these ventilatory efforts increasingly vigorous [25], and the related decreases in arterial pressure consequently larger [42]. The inspiratory efforts reduce pleural pressure, which increases left ventricular afterload [35] and reduces left ventricular emptying. At the same time, the decrease in pleural pressure results in an increase in right atrial transmural pressure, accompanied by increased venous return [26]. The increase in atrial transmural pressure stimulates release of atrial natriuretic peptide, which probably causes the sleeping natriuresis of untreated obstructive sleep apnoea [39]. In normal supine man, the increase in venous return caused by the decreases in pleural pressure may be limited by the collapse of the major veins carrying blood into the thorax [10, 46]. The increased venous return that does occur distends the right ventricle, which reduces left ventricular compliance [65]. This impairs left ventricular filling and ejection. Finally, changes in intrathoracic pressure alter lung blood content in a way which is difficult to predict if the lung volume changes [8]. However, during obstructive sleep apnoea lung volume is fixed, the airway blocked and decreases in pleural pressure are mirrored by decreases in alveolar pressure. In this situation, lung blood volume probably increases [8].

At the end of an obstructed inspiratory effort, these effects are reversed. One obstructive apnoea includes a series of transient inspiratory efforts; how much recovery occurs between efforts is uncertain, and probably varies between subjects. These opportunities for recovery are often overlooked, and one apnoea is discussed as if it were a single sustained Müller manoeuvre. In support of this assumption, a progressive leftward shift in the ventricular septum occurs throughout an apnoea [58], although this may be the result of a progressive increase in right ventricular afterload because of hypoxic pulmonary artery vasoconstriction. Left ventricular end-diastolic and pulmonary capillary wedge pressures also increase throughout an apnoea [9] and cardiac output decreases [23, 65]. After an episode of apnoea, an increase in arterial pressure occurs [55]; the reversal of the haemodynamic effects of the apnoeic period and the consequent release of a bolus of blood from the thorax probably contribute to this.

Superimposed on the mechanical effects of the obstructed inspiratory efforts are the actions of hypoxia and hypercapnia. Hypoxia contributes directly to apnoeic bradycardia [70] and arrhythmias [56] and may also have a role in the apnoea-related increases in arterial pressures [55], although this is controversial. It is clear that the apnoea-induced nadir in arterial oxygen saturation coincides with the peak of the post-apnoeic increase in arterial pressure and correlates with its magnitude [4, 55]. Furthermore, obstructive sleep apnoea simulated during wakefulness causes arterial pressure changes which are attributable to hypoxia [1]. However, it is not clear that this effect persists during sleep. Two recent studies have corrected the arterial desaturation of obstructive sleep apnoea with supplementary oxygen without halting the apnoea–arousal cycle [4, 52]. In both these studies, abolishing hypoxaemia did not alter the magnitude of the increase in arterial pressure after the apnoeic episode. Furthermore, sleeping hypoxaemia as severe as that seen during obstructive sleep apnoea, but produced without apnoea or arousal, does not cause an increase in arterial pressure [52].

Hypercapnia also is unlikely to be a major contributor to the haemodynamic instability of obstructive sleep apnoea, as the changes in arterial partial pressures of carbon dioxide are small. After apnoea with airway closure, the alveolar partial pressure of carbon dioxide equilibrates with mixed venous values within one circulation time—less than 1 min [47]. Assuming normal indices before apnoea, this leads to an increase in the arterial partial pressure of carbon dioxide from 5.3 to 6.1 kPa; thereafter the value increases by about 0.4–0.8 kPa min^{-1} [47], reflecting changes in the total body carbon dioxide stores. Over 2 min, this increases the partial pressure by about 1.4 kPa. Typically, the obstructive sleep apnoea cycle lasts about 1 min, of which 25% comprises ventilation; an increase in Pa_{CO_2} of 1.4 kPa is thus an overestimate of the change that would be expected. In dogs, increasing Pa_{CO_2} by 1.4 kPa increases arterial pressure by only about 5 mm Hg [53]. The average post-apnoeic arterial pressure increase associated with obstructive sleep apnoea is about 20 mm Hg [55]; increases as great as 100 mm Hg may occur.

The third element of the obstructive sleep apnoea cycle which is capable of causing much of the post-apnoeic haemodynamic response is arousal from sleep at the end of apnoea [14]. Arousal from normal sleep causes a range of responses which include skin vasoconstriction [69], increased heart rate [34], changes in skin resistance [34] and an increase in arterial pressure [14]. The magnitude of these responses varies with the duration of EEG arousal [14], and does not habituate with repetition [34, 69]. Together, these responses have been termed the orienting reflex [34]. The magnitude of the arterial pressure response to arousal from normal sleep may be similar to that observed with arousal during obstructive sleep apnoea [14], and is preserved in obstructive sleep apnoea patients who have been treated effectively with nasal continuous positive airway pressure [52]. Further support for an important contribution from arousal comes from sleep disruption syndromes which include arousal and cause changes in arterial pressure, but which lack other features of obstructive sleep apnoea. In central sleep apnoea, periodic ventilation and arousal occur without obstructed respiratory efforts [25] and in periodic movements of the legs, recurrent arousal occurs without any ventilatory respiratory abnormality [45]. Both these syndromes cause changes in arterial pressure similar to those of obstructive sleep apnoea [3, 12].

Obstructive sleep apnoea is also associated with substantial autonomic nervous system activation. During each period of apnoea there is a progressive increase in peripheral neural sympathetic [28] and cardiac vagal [64] activity, which terminates abruptly at the resumption of breathing [28]. Urine catecholamine concentrations are increased markedly at night, and probably abnormal also during the day—changes which resolve with effective treatment [17].

Chronic effects of obstructive sleep apnoea

The long-term adverse effects of obstructive sleep apnoea are the result of sleep disruption and cardiorespiratory disease. The 300 or more arousals which occur during every night of severe obstructive sleep apnoea severely fragment sleep and cause marked daytime sleepiness [25]. Tasks which require sustained vigilance (particularly driving) are badly affected—untreated sleep apnoea sufferers are 5–10 times more likely than normal individuals to be involved in road traffic accidents [16, 18]. The heavy snoring at night and daytime hypersomnolence cause significant social distress, and the inability to remain awake at work may lead to loss of employment.

A small minority of obstructive sleep apnoea patients with another respiratory impairment develop daytime respiratory failure and cor-pulmonale [40]—the "Pickwickian Syndrome". In adults, the associated respiratory abnormality is usually chronic obstructive lung disease [7, 40], although a restrictive lung defect from morbid obesity and neuromuscular weakness are other possibilities. In this situation, provided the second respiratory illness is not itself severe, respiratory failure improves when the obstructive sleep apnoea is treated effectively [6]. Children may also develop pulmonary hypertension [68] and perioperative deaths from corpulmonale as a result of obstructive sleep apnoea have been reported after adenotonsillectomy [68].

Untreated adult obstructive sleep apnoea is associated with vascular death [48], daytime hypertension [21] and coronary artery disease [30]. However, interpretation of these associations is complex because patients with obstructive sleep apnoea and snoring tend to be obese and have large intakes of tobacco and alcohol. Relatively few studies have corrected adequately for these confounding variables [59, 67].

TREATMENT OF OBSTRUCTIVE SLEEP APNOEA

Pharyngeal and craniofacial surgery [51, 57], tracheotomy [48] and weight loss [48] have all been used in the chronic management of obstructive sleep apnoea. However, nasal continuous positive airway pressure [62] has recently become the mainstay of adult chronic management, and is also appropriate for the hospital inpatient with obstructive apnoea not corrected by changing from a supine posture. Increasing the intrapharyngeal airway pressure forces the airway open by acting as a pneumatic splint [50]; this corrects the apnoea [62], the associated snoring [62] and the cardiovascular and autonomic instability [4]. A nasal mask may be used, which is less claustrophobic than a full face mask, although in some subjects a substantial mouth leak necessitates a chin support. Side effects of this treatment are few. Nasal obstruction and rhinorrhea may occur, but usually respond to nasal decongestants. Cardiac output may decrease when airway pressure is increased [37], and this should be considered when patients with severe cardiac disease are treated.

Hospital inpatients who have previously been treated for obstructive sleep apnoea should continue their usual treatment during their admission. Many will have their own nasal continuous positive airway pressure machine which can be brought into hospital. These machines are light and portable, and require only a mains power supply. Supplementary oxygen may be added to the nasal mask if needed, although this delivers an unpredictable inspired concentration of oxygen. The continued use of continuous positive airway pressure is particularly important if substantial haemodynamic lability is disadvantageous, such as after vascular surgery.

Oxygen therapy alone is inadequate treatment. Sleep apnoea-induced hypoxaemia may be corrected in this way [4, 52], but many of the other effects are not returned to normal. The disturbances in pleural pressure, cardiac preload and afterload, heart rate, arterial pressure and sleep structure, all persist unless airway patency is maintained [4, 52].

Subjects who require treatment for obstructive sleep apnoea during an acute illness or perioperatively should all be assessed for persisting apnoea after their recovery. A proportion of these subjects may have continuing problems which require appropriate long-term management.

CONCLUSION

Obstructive sleep apnoea is a common disorder. About one in 50 men have some upper airway obstruction when lying supine, and this is worse under the provocation of sedative or neuromuscular blocking drugs. Untreated obstructive sleep apnoea produces potentially disadvantageous blood-gas, haemodynamic and autonomic changes, all of which are corrected with continuous positive airway pressure. Awareness of obstructive sleep apnoea is needed among medical staff treating acutely ill hospital patients.

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SHORT COMMUNICATIONS

RECOVERY OF ATRACURIUM AND VECURONIUM NEUROMUSCULAR BLOCK IN THE ISOLATED FOREARM

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SUMMARY

The duration of recovery from neuromuscular block after a $3 \times ED_{90}$ dose of atracurium or vecuronium is similar in spite of a three-fold difference in their elimination half-lives. We have investigated simultaneous spontaneous recovery from equipotent doses of atracurium and vecuronium in the isolated forearms of volunteers in order to attempt to explain this paradox. Simultaneous administration of the two drugs, one in each of the subject's forearms, allowed direct comparison of recovery to be made against the same plasma concentration of drug. The recovery index of atracurium was found to be significantly longer than that of vecuronium. We suggest that this observation, when considered with the different plasma concentrations after a $3 \times ED_{90}$ dose, helps to explain the similar duration of action of the two drugs during the recovery phase after a large systemic bolus. (Br. J. Anaesth. 1993; **71**: 730–731)

KEY WORDS

Neuromuscular relaxants: atracurium, vecuronium, isolated forearm, recovery rate.

The duration of neuromuscular block produced by a single bolus dose of $3 \times ED_{90}$ of vecuronium or atracurium is similar [1, 2]. However, the clearance of the two drugs differs three-fold, producing a faster rate of reduction in the plasma concentration of atracurium than vecuronium during recovery from neuromuscular block. Bowman [3] and Bevan, Bevan and Donati [4] have pointed to this as a paradox that is difficult to explain by simple pharmacokinetic events. It has been suggested that, because of the metabolism of atracurium, there is a different treatment of both drugs in the effect compartment [4, 5]. However, there is no evidence that this occurs *in vivo* [6]. Various pharmacokinetic models have been constructed in an attempt to explain this phenomenon.

We have studied spontaneous recovery from equipotent doses of atracurium and vecuronium administered simultaneously, one drug in each of the two isolated forearms of volunteers. This technique allowed us to compare the recovery from neuromuscular block produced by the drugs against the same minimal non-blocking plasma concentration. In this way, recovery from neuromuscular block can be separated from the effect of changes in plasma concentration of the drug.

METHODS AND RESULTS

We studied the spontaneous recovery of atracurium and vecuronium neuromuscular block in the isolated forearm in eight investigations in six volunteers (29–61 yr). Ethics Committee approval for the study was obtained.

A vein at the back of each hand was cannulated. Bilateral forearm tourniquets were applied. The ulnar nerve at the wrist was stimulated via surface electrodes. Supramaximal pulses of 0.2 ms duration were delivered by a nerve stimulator at a frequency of 0.2 Hz. The resultant force of thumb adduction was monitored by a force displacement transducer preloaded to 200 g.

After a period of stabilization of 10 min the forearm tourniquets were inflated simultaneously to 300 mm Hg pressure. Vecuronium 0.3 mg diluted in saline 20 ml was injected i.v. into the back of one hand and atracurium 1.5 mg diluted in saline 20 ml into the other hand. These are equipotent doses and each drug produced the same degree of neuromuscular block in the isolated forearm. The forearm tourniquets were released simultaneously after 3 min. In all experiments, greater than 90% twitch depression was achieved. We excluded from the results any experiment in which a block greater than 99% occurred. The recovery indices (RI) (time from 25% to 75% recovery) for both drugs were measured, as was the time from 0% to 25% twitch recovery. The mean RI of atracurium and vecuronium were compared using Student's paired *t* test.

All volunteers were healthy and none was receiving any medication influencing neuromuscular conduction. Similar degrees of block were produced in both arms. The block for vecuronium was 97.6 (SD 1.4)% and that for atracurium 94 (1.8)%.

Mean (SD) time from maximum block to 25% recovery was 17.6 (6.8) min for atracurium and 13.3 (2.7) min for vecuronium. Mean 25–75% RI for

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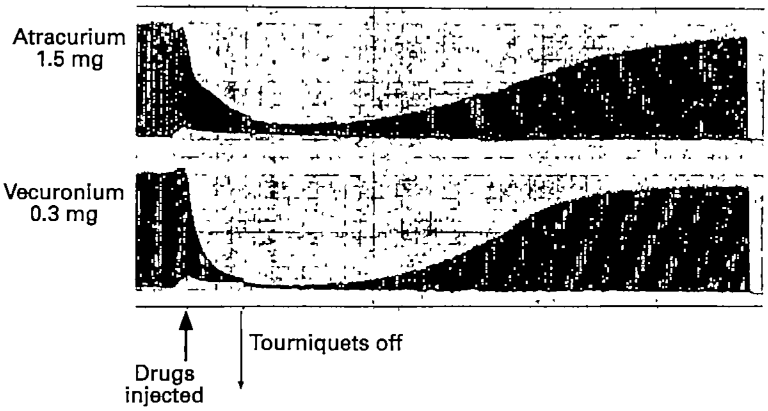

FIG. 1. Typical trace of onset and recovery of neuromuscular block in the two arms of a volunteer after simultaneous administration of atracurium 1.5 mg in saline 20 ml (upper trace) in one isolated forearm and vecuronium 0.3 mg in saline 20 ml (lower trace) in the other. The tourniquet was released at 3 min. The RI of vecuronium is shorter than that of atracurium.

vecuronium was 7.9 (0.85) min (range 6.9–9 min) and for atracurium 10.6 (1.8) min (range 8.3–13.6 min) ($P = 0.004$).

COMMENT

Bevan, Bevan and Donati [4] asked "why are the duration of action and rate of recovery from atracurium and vecuronium similar when their elimination half-lives differ threefold?" It is this question that we have examined.

The previous suggested explanation, that the metabolism of atracurium in the effect compartment could explain this paradox, is improbable as the effect compartment is of small size and Ericksson and colleagues [6] have demonstrated that Hofmann degradation does not occur to any extent at the neuromuscular junction.

In these experiments, we have demonstrated that vecuronium is associated with a significantly shorter time to spontaneous recovery from neuromuscular block than atracurium (7.9 *vs* 10.6 min) in the isolated forearm. By using simultaneous administration of the two drugs, we subjected each arm to similar circulation changes and to the same plasma concentration of both drugs. If any degradation of atracurium had occurred during the period of tourniquet occlusion, when the biophase concentration would have been great, the recovery of atracurium block recorded would have underestimated the effect of the drug.

We have demonstrated previously that the systemic effect of doses of neuromuscular blocking drugs of this magnitude do not affect recovery in the isolated arm. It has been demonstrated that, when drugs of similar clinical duration of action and similar pharmacokinetic profiles are compared in the isolated arm there is no difference in their RI. It has been proposed that different recovery times revealed in the isolated arm reflect different affinities with biophase binding sites.

We can now suggest an explanation as to why the recovery times of atracurium and vecuronium are similar after systemic $3 \times ED_{90}$ doses. If the plasma concentrations of both drugs were similar during the elimination half-life, one would expect vecuronium to recover more quickly than atracurium (indeed there is evidence that this occurs following $1 \times ED_{90}$ to $1 \times ED_{95}$ of both drugs). However, if the plasma–biophase concentration gradient of vecuronium were reduced by a greater concentration of drug in the plasma, the spontaneous recovery rate would be slower and likely to approach that of atracurium. Thus the inherently faster spontaneous recovery of vecuronium neuromuscular block in the isolated forearm is offset by the effect of the greater plasma concentration of drug during the elimination phase. We suggest that this mechanism explains the similar duration of action of these two drugs when used in clinical doses as bolus injections.

ACKNOWLEDGEMENT

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British Journal of Anaesthesia 1993; 71: 732–733

MUSCLE FIBRE DIAMETER AND SENSITIVITY TO NEUROMUSCULAR BLOCKING DRUGS

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SUMMARY

In order to investigate the relationship between muscle fibre composition or size and muscle sensitivity to neuromuscular blocking drugs, data on the fibre composition and size of the ulnaris lateralis, thyroarytenoideus, cricoarytenoideus dorsalis and diaphragm muscles of the goat were related to the rate of recovery of these muscles from suxamethonium or vecuronium block. Muscle sensitivity (time to spontaneous 25% recovery of evoked EMG response after 100% block) correlated well with fibre size, the association being significant for the diameter of type I ($r \geqslant 0.94$*;* $P \leqslant 0.016$*) and types I and II fibres taken together (*$r \geqslant 0.95$*;* $P \leqslant 0.013$*), but not for type II fibre diameter (*$r \leqslant 0.83$*;* $P \geqslant 0.084$*), for both suxamethonium and vecuronium. There was no association between the composition of types I or II fibres in these muscles and sensitivity (*$r \leqslant 0.37$*;* $P \geqslant 0.546$*). This suggests that muscle sensitivity to both depolarizing and non-depolarizing drugs increases with fibre size, and may account partly for the unequal sensitivities of different muscles.* (Br. J. Anaesth. 1993; **71**: 732–733)

KEY WORDS

Neuromuscular transmission: nerve fibres. Neuromuscular relaxants: suxamethonium, vecuronium.

Although it has long been known that mammalian striated muscles differ in their sensitivity to neuromuscular blocking drugs, the reasons remain poorly understood. Possible mechanisms proposed include differences between muscles in perfusion, temperature, number and affinity of acetylcholine receptors, the dissociation rate constant of the drug–receptor complex, acetylcholinesterase activity, fibre type composition or fibre size [1]. While some of these hypotheses have been disproved, others do not appear plausible or have not been investigated in detail. In this study, we have investigated the contributions of differences in fibre composition and size to the unequal sensitivities of muscles to neuromuscular blocking drugs.

METHODS AND RESULTS

The studies were carried out under Project Licence PPL 80/00174 of the Home Office, using adult female British Saanen breed of goats. Muscle specimens were taken from the ulnaris lateralis, thyroarytenoideus, cricoarytenoideus dorsalis and diaphragm of four goats, the fibres differentiated into types I and II by enzyme histochemistry and the composition and diameter of each type in each muscle determined by computerized planimetry [2]. In another study, two groups each of five similar goats were used for studies on suxamethonium or vecuronium. The animals were anaesthetized with thiopentone and halothane in oxygen and the lungs ventilated mechanically to maintain normocapnia. The ulnaris lateralis, thyroarytenoideus, cricoarytenoideus dorsalis and diaphragm muscles were stimulated indirectly via their motor nerve supply with supramaximal stimuli at 1 Hz and the evoked electromyographic response monitored. I.v. doses of suxamethonium 500 $\mu g\ kg^{-1}$ or vecuronium 4 $\mu g\ kg^{-1}$, producing complete paralysis in the four muscles, were administered and the time from injection to spontaneous recovery of evoked EMG response to 25% of control noted.

The relationship between the mean composition and diameter of types I and II fibres in the various muscles studied and the relative sensitivities of the muscles to suxamethonium or vecuronium (as reflected by the time for spontaneous recovery of evoked response to 25% of control after 100% block) was investigated by correlation analysis. $P \leqslant 0.05$ was taken to indicate statistical significance.

There was an association between time to spontaneous 25% recovery from either vecuronium or suxamethonium block and fibre diameter, the association being significant for the diameter of type I and types I and II fibres taken together, but not for type II fibre diameter. There was no association between muscle fibre composition and time to 25% recovery from each neuromuscular blocker (table I).

COMMENT

These data suggest that muscle sensitivity to neuromuscular blocking drugs might be related to fibre size in such a way that sensitivity to either depolarizing or non-depolarizing blockers increases with fibre size but, like the unequal sensitivities of different muscles to these drugs, the mechanisms underlying this association are not clear. Although

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TABLE I. *Mean* (SD) *composition* (*Comp.* %) *and diameter of types I and II fibres in the ulnaris lateralis, diaphragm, thyroarytenoideus and cricoarytenoideus dorsalis muscles of the goat, and their association* (*correlation coefficient* r *and probability* P) *with time to 25% spontaneous recovery of evoked response after suxamethonium 500* $\mu g\ kg^{-1}$ *or vecuronium 4* $\mu g\ kg^{-1}$

Muscle	Type I fibre (Comp. (%))	Fibre diameter (μm)		
		Type I	Type II	Types I & II
Ulnaris lateralis	41.96 (0.01)	61.5 (12.6)	53.8 (5.9)	56.4 (8.1)
Diaphragm	58.12 (10.68)	40.5 (8.4)	36.6 (9.8)	38.6 (9.3)
Thyroarytenoideus	29.56 (3.58)	30.7 (7.5)	40.5 (7.5)	35.6 (7.5)
Cricoarytenoideus dorsalis	42.44 (5.04)	30.6 (6.3)	37.4 (5.8)	34.0 (5.9)
Correlation with 25% recovery (*r* (*P*))				
Suxamethanium	0.37 (0.546)	0.99 (0.001)	0.73 (0.164)	0.95 (0.012)
Vecuronium	0.02 (0.978)	0.94 (0.016)	0.83 (0.084)	0.97 (0.008)

alterations in muscle fibre acetylcholine receptor population may account for changes in muscle sensitivity to neuromuscular blocking drugs under a wide variety of physiological and pathological conditions [3], differences in acetylcholine receptor population or density *per se* may not account for either the unequal sensitivities of normal muscles to neuromuscular drugs or the presently demonstrated association between fibre size and muscle sensitivity. If these phenomena were related to acetylcholine receptor population or density, a reciprocal relationship would exist between the response of a muscle to depolarizing and non-depolarizing drugs on the basis of the current theories relating to the mechanisms of action. Consideration of the sensitivities of the diaphragm and adductor pollicis muscles to suxamethonium and vecuronium shows that this is not so [1, 4].

Instead, the unequal sensitivities of normal muscles might be related to differences between muscles in fibre size, the latter being related directly to the size and complexity of the neuromuscular junction [5], but it is not clear if and how the size of the neuromuscular junction relates to acetylcholine receptor characteristics. It may be that acetylcholine receptors on small and large fibres differ in characteristics such as their affinity for neuromuscular blocking drugs and the dissociation rate constant of the drug–receptor complex. These possibilities and the role, if any, of differences in acetylcholinesterase activity and acetylcholine receptor population and density at neuromuscular junctions in different muscles deserve investigation.

The association between fibre size and muscle sensitivity demonstrated in this study suggests that peripheral muscles composed of small calibre fibres may be reliable guides for monitoring profound paralysis in laryngeal muscles and the diaphragm. This association may account for the similarities in sensitivity between the orbicularis oculi, diaphragm and laryngeal adductor muscles, all of which are composed of small calibre fibres; together with similarities in perfusion, this may explain why the orbicularis oculi muscle is a better guide than the adductor pollicis muscle for monitoring the course and degree of paralysis in laryngeal adductor muscles and the diaphragm [4, 6].

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COMPARISON OF END-TIDAL AND ARTERIAL CARBON DIOXIDE MEASUREMENTS DURING ANAESTHESIA WITH THE LARYNGEAL MASK AIRWAY

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SUMMARY

We have confirmed the value of measurement of end-tidal carbon dioxide concentration as an indicator of arterial carbon dioxide tension during the use of the laryngeal mask airway in healthy patients breathing spontaneously. The mean difference between arterial and end-tidal carbon dioxide tension was 0.52 kPa (range 0–1.5 kPa), which is similar to the difference which has been reported when a tracheal tube has been used. (Br. J. Anaesth. 1993; **71**: 734–735)

KEY WORDS

Anaesthesia: general. Airway: laryngeal mask. Monitoring: end-tidal carbon dioxide.

Amongst the advantages of the use of the laryngeal mask airway (LMA) is the ability to measure end-tidal carbon dioxide concentration, which has always been difficult when the face mask is used.

Measurement of end-tidal carbon dioxide concentration in patients breathing spontaneously with a tracheal tube has been examined in the past and the relationship between arterial and end-tidal carbon dioxide has been described [1]. In this system, there is an airtight seal between the tube and the patient, while with the LMA the orifice and cuff are opposed to the larynx and the reliability of the seal is always in doubt. If air entrainment or mixing occurs, the accuracy and reliability of the end-tidal carbon dioxide measurement must be questioned. We have therefore compared the end-tidal carbon dioxide partial pressure (PE'_{CO_2}) during anaesthesia with an LMA and that in arterial blood (Pa_{CO_2}).

METHODS AND RESULTS

After obtaining local Ethics Committee approval and informed patient consent, we studied patients undergoing routine minor operations without respiratory disease who would normally be anaesthetized using an LMA. Premedication and induction were as designated by the anaesthetist in charge, as were the inhalation agent and breathing system. A size 3 mask for females and size 4 for males was used generally. The LMA was inserted, positioned and tested as recommended in the instruction manual. The carbon dioxide analyser was attached directly to the proximal end of the LMA; a catheter mount was not used. When a reasonably steady state of anaesthesia was reached, a blood sample was obtained from the radial artery for analysis (Instrumentation Laboratory 1312 Blood Gas Manager). The analyser underwent two-point calibration before each study and had an accuracy to within 0.02 kPa of carbon dioxide. Pa_{CO_2} was compared with the simultaneous end-tidal carbon dioxide partial pressure measured digitally from the plateau phase on a Hewlett–Packard capnograph (Hewlett–Packard Component Monitoring System, M1049-90001), in keeping with usual clinical practice. The capnograph (a main stream analyser), was auto-calibrated before each study using the two standard cells containing known concentrations of carbon dioxide. Its stated accuracy is ±0.15 kPa.

Data were analysed using Statview 4.0 (Abacus Concepts Inc). Correlation was evaluated using Fisher's *R–Z* method and the data were assessed further using the method of Bland and Altman [2]. Multiple regression analysis (Statview 4.0) was used to determine the influence of the other factors including ASA grade, weight, age and smoking habit.

We studied 122 patients (30 male, 92 female; mean weight 67 kg (range 43–120 kg); 94 were ASA I, 23 ASA II and five ASA III; 32 known smokers).

Propofol was used as induction agent in all but seven patients and isoflurane as the inhalation agent in all patients. Analgesics used included opioids, non-steroidal anti-inflammatory agents and local anaesthetic techniques. Sixty-one patients were anaesthetized using the Magill breathing system, 41 with the Bain system and 20 with the circle system.

Mean (SD) Pa_{CO_2} was 6.50 (0.9) kPa (range 4.85–9.70 kPa). Mean PE'_{CO_2} was 5.96 (0.92) kPa (range 4.25–8.40 kPa). Mean arterial to end-tidal carbon dioxide difference ($Pa_{CO_2} - PE'_{CO_2}$) was 0.52 (0.32) kPa (range 0–1.5 kPa).

The correlation coefficient between PE'_{CO_2} and Pa_{CO_2} was 0.923 (Fisher's *R–Z* statistic, $P < 0.0001$).

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Using the method of Bland and Altman [2] comparing the mean and the difference of the two methods, the correlation was 0.027. When the correlation was assessed with each breathing system, no obvious difference emerged. The difference between arterial and end-tidal carbon dioxide was evaluated also by multiple regression to assess the influence of ASA grade, weight and age, but there was no obvious disparity. Smoking in these predominately ASA I and II patients did not influence the results.

COMMENT

The majority of patients in whom anaesthesia with spontaneous breathing is used are ASA I and II and this study suggests that end-tidal carbon dioxide measured at the end of the LMA correlates well with arterial carbon dioxide in these patients.

In normal lungs, the end-tidal gas is considered to be in equilibrium with pulmonary capillary blood and this assumption is extrapolated to use the partial pressure of end-tidal carbon dioxide ($P\text{E}'_{CO_2}$) as an indirect measure of arterial carbon dioxide (Pa_{CO_2}). This is not necessarily correct, and several studies have examined this during both spontaneous and artificial ventilation. In these studies, a tracheal tube has usually been used and the measurements of end-tidal carbon dioxide taken from the proximal end of the tracheal tube [1, 3]. Measurement of end-tidal carbon dioxide while a face mask is in place is feasible, but unreliable, and is not applicable in clinical practice.

Nunn and Hill studied anaesthetized patients with an intubated trachea and showed that the mean (SD) ($Pa_{CO_2}-P\text{E}'_{CO_2}$) was 0.61 (0.33) kPa and this appeared to be independent of the mode of ventilation [1]. This value was comparable to that of 0.52 (0.32) kPa found in this study, in which patients breathed spontaneously.

The results obtained by Nunn and Hill [1] have been corroborated in some studies and refuted by others [3–6]. These studies involved small numbers of predominantly ASA III patients undergoing anaesthesia, or critically ill patients in Intensive Care. This is hardly surprising, for several reasons. Measurement problems include difficulty in achieving and recognizing a genuine end-tidal carbon dioxide plateau in patients with significant lung pathology, so there is no measurable end-tidal value. This problem may be accentuated if a side-stream analyser is used, when ventilatory pattern and frequency may result in mixing which influences the ability of the analyser to determine an end-tidal value. The pathophysiology of many lung diseases is likely to alter the relationship between arterial blood-gas tension and representative capillary tensions, and the relationship between the capillary tensions and the end-tidal value. The assumption that end-tidal gas tensions represent capillary gas tensions and that these represent arterial blood-gas tensions is not valid. Data from critically ill patients demonstrate that there is no predictable relationship between arterial and end-tidal carbon dioxide tensions [5, 6] and, while it has been suggested that the trend values may be helpful, Hoffman and colleagues have shown that the use of $P\text{E}'_{CO_2}$ as a monitor of Pa_{CO_2} as a trend value is misleading, even after the establishment of an initial ($Pa_{CO_2}-P\text{E}'_{CO_2}$) gradient [6].

It is reasonable to assume that the end-tidal carbon dioxide values in the presence of lung disease are as unreliable with an LMA as with a tracheal tube. However, we have demonstrated that, in anaesthetized ASA grade I and II patients breathing spontaneously via an LMA, $P\text{E}'_{CO_2}$ is a reasonable indicator of Pa_{CO_2}. Measurement of end-tidal carbon dioxide did not appear to be disturbed functionally by the absence of the airtight seal which is present when a tracheal tube is used.

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EFFECT OF ATROPINE ON THE QT INTERVAL AND T-WAVE AMPLITUDE IN HEALTHY VOLUNTEERS

P. ANNILA, A. YLI-HANKALA AND L. LINDGREN

SUMMARY

Prolongation of the QT interval of the ECG represents an imbalance in cardiac autonomic function and may predict cardiac arrhythmia. Vagal activity protects against prolongation of the QT interval which may be associated with flattening of the T-wave of the ECG. The changes in QT interval, T-wave amplitude and respiratory sinus arrhythmia (RSA) were studied after i.v. administration of atropine 20 $\mu g\ kg^{-1}$ or placebo to 10 healthy volunteers in a cross-over study. After atropine, a decrease in RSA occurred in all volunteers, but remained at baseline values after placebo. Corrected QT interval (QTc) increased from 410 (20) ms to 454 (11) ms ($P < 0.001$*) 5 min after atropine and remained prolonged for the entire study period (60 min). The T-wave flattened significantly (measured as R:T ratio) up to 30 min, without any changes in the R-wave. No changes in the ECG occurred with placebo.* (Br. J. Anaesth. 1993; **71**: 736–737)

KEY WORDS

Parasympathetic nervous system: atropine. Heart: ECG.

Imbalance in cardiac autonomic function (increased sympathetic activity) prolongs the QT interval of the ECG, reflecting the rate of myocardial repolarization [1]. Prolongation of the QT interval has been shown to be a prognostic sign for cardiac arrhythmia. It occurs in the presence of increased concentrations of circulating catecholamines. When sympathetic tone predominates, vagal stimulation is believed to protect the ventricular myocardium by stabilizing the heart electrically [2]. Changes in the amplitude of the T-wave may be related to changes in the QT interval.

Cardiac arrhythmia has been reported after administration of atropine during induction of anaesthesia [3]. This may result from reduction in vagal protection and prolongation of the QT interval. The effect of atropine on the QT interval and on the T-wave amplitude has not been systematically evaluated, therefore we studied the effect of atropine on these variables in healthy volunteers in a placebo-controlled cross-over study.

METHODS AND RESULTS

The study was approved by the Ethics Committee of the Fourth Department of Surgery. Ten volunteers (four female and six male; mean age 31 (SD 3.4) yr (range 24–35 yr); weight 66 (11.4) kg) gave informed consent.

A vein of the dorsum of the hand was cannulated and the subject rested in the supine position for 10 min before beginning the study. The ECG was amplified from lead V_2 using an Olli 435D (Kone Ltd, Finland) monitor, recorded on tape (Racal FM tape recorder, Racal Ltd, England) and digitized off-line at 200 samples s^{-1} channel^{-1} into a PC-compatible microcomputer.

A deep breathing test was used to evaluate respiratory sinus arrhythmia (RSA). The volunteer was asked to breathe using a maximal tidal volume at a rate of 6 b.p.m. The difference between the maximum and the minimum heart rates during a ventilatory cycle was calculated. The initial deep breathing test was followed by atropine 20 $\mu g\ kg^{-1}$ i.v. and was then repeated 5 min and 60 min later. The ECG was recorded until the last RSA test was performed. In seven of the 10 subjects, the trial was repeated using physiological saline as a placebo. All tests were performed between 15:00 and 18:00.

QT intervals were calculated from the ECG printed on paper. The corrected QT interval (QTc) was measured from four consecutive complexes according to Bazett's formula ($QTc = QT/\sqrt{R-R'}$) at rest, 5, 30 and 60 min after administration of atropine or placebo. The ratio of the amplitude of R-peaks and T-waves (R:T ratio) was calculated as a mean of three consecutive complexes. All amplitudes were measured during expiration (maximum R-peak amplitude) at rest, 5, 30 and 60 min after i.v. atropine or placebo.

Statistical evaluation between groups was performed using two-way analysis of variance. Changes within a group were tested with one-way analysis of variance corrected by Fisher PLSD test. Statistical analysis was performed using Stat View 512+® software (Brain Power Inc., Calabasas, CA, U.S.A.). $P < 0.05$ was considered statistically significant. Results are presented as mean (SD).

Heart rate increased from 64 (10) beat min^{-1} to 94 (11) beat min^{-1} 5 min after atropine ($P < 0.001$). At

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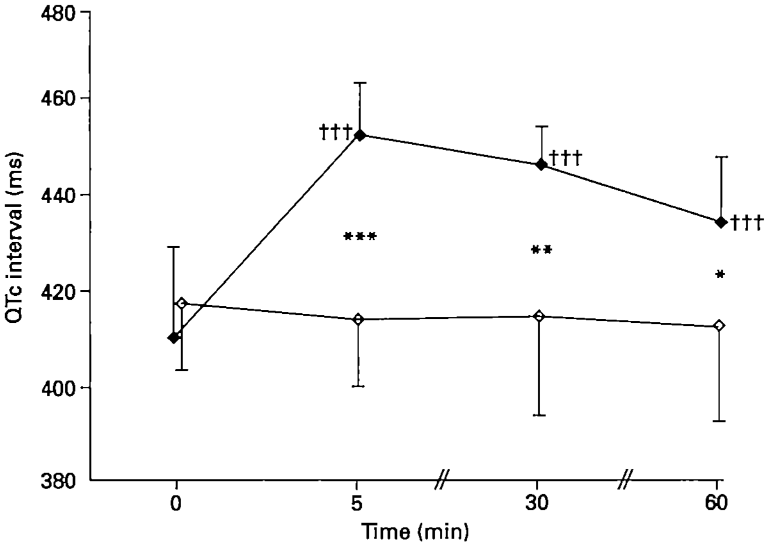

FIG. 1. QTc interval (mean, SD). ◆ = Volunteers (10) receiving atropine 20 μg kg^{-1}; ◇ = seven of the same volunteers receiving placebo. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ between groups (two-way ANOVA). $†††P < 0.001$ from baseline within a group (one-way ANOVA).

30 min it was 92 (13) beat min^{-1} and at 60 min 82 (11) beat min^{-1} ($P < 0.001$). After atropine, the QTc interval increased significantly from baseline at each measurement point ($P < 0.001$) (fig. 1). Each subject had normal (> 12 beat min^{-1}) RSA before administration of the test drugs. Five minutes after atropine, RSA was greatly reduced (4 (1.6) beat min^{-1}) ($P < 0.001$); 60 min after atropine, it was 9.8 (3.8) beat min^{-1} ($P < 0.001$). Five minutes after atropine, the R:T ratio increased from 1.15 (0.4) to 1.40 (0.6) ($P < 0.01$); at 30 min it was 1.51 (0.7) ($P < 0.001$) and at 60 min it was 1.33 (0.5) ($P < 0.05$). The R-wave amplitude was not affected by atropine. No changes in heart rate, QTc interval, RSA and R:T ratio occurred after placebo.

COMMENT

These data show that, in the presence of vagal block by atropine, the QTc interval increased significantly and the T-wave of the ECG was flattened.

We chose a relatively large dose of atropine to ensure parasympathetic block as confirmed by the disappearance of RSA. Day, McComp and Campbell [1] have suggested that QT dispersion (interlead variability) gives an indication of arrythmogenicity and repolarization. We used a single lead V_2 which, according to the same group, provides the closest approximation to maximum QT interval [4]. They also accept the validity of a single lead value for QTc when changes are monitored. The flattened T-wave after atropine in our volunteers probably also reflected irregularity in repolarization.

Atropine has been shown to increase the incidence of cardiac arrhythmia during induction of anaesthesia [3]. In addition, i.v. atropine has been shown to cause ventricular tachycardia in a patient with a prolonged QT interval syndrome [5]. Inhibition of the sympathoadrenal tone by opioids shortens the QTc interval in patients with vagal block. Vagal stimulation protects the heart against arrhythmogenic vulnerability [2] and against prolongation of the QT interval. In our study, the QTc interval was prolonged, probably because sympathoadrenal tone became dominant after parasympathetic block by atropine.

In diabetic patients, vagal denervation develops gradually. Maintenance of remaining borderline vagal function by avoiding anticholinergics may be of value in diabetic patients, as serious cardiac arrhythmia has been described in these patients during anaesthesia and after atropine. Furthermore, ventricular fibrillation after i.v. atropine for bradycardia has been shown to occur in acute myocardial infarction [6]. The routine use of anticholinergics at induction of anaesthesia must be seriously questioned.

ACKNOWLEDGEMENT

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British Journal of Anaesthesia 1993; 71: 738–740

CASE REPORT

NORPETHIDINE TOXICITY AND PATIENT CONTROLLED ANALGESIA

P. A. STONE, P. E. MACINTYRE AND D. A. JARVIS

SUMMARY

Patient-controlled analgesia (PCA) with i.v. opioids is prescribed increasingly. We report three cases of norpethidine toxicity in patients receiving pethidine by PCA. (Br. J. Anaesth. 1993; **71**: 738–740)

KEY WORDS

Analgesia: patient-controlled. Opioids: pethidine. Complications: norpethidine toxicity.

CASE REPORTS

Patient No. 1

A 61-yr-old, 54-kg female was admitted for closure of ileostomy, 4 months after a right-hemicolectomy for angiodysplasia. She had a history of chronic obstructive airways disease and chronic hip pain. There was no history of convulsions. Her long-term drug therapy comprised theophylline, salbutamol, inhaled steroids, amitriptyline, carbamazepine, frusemide and somatostatin. The carbamazepine was prescribed for her chronic hip pain. She said that she wheezed if given morphine. Eleven days after closure of the ileostomy, she required a laparotomy and repeat ileostomy for an anastomotic leak.

Extradural pethidine was used for analgesia for 4 days after the closure of ileostomy, followed by intermittent i.m. pethidine. After the laparotomy, i.v. pethidine by PCA was commenced.

The day after the laparotomy, the patient was noted to be anxious and to have a tremor, and she had an episode of rhythmic twitching. She was treated with i.v. diazepam 3 mg. At 36 h after starting PCA, she received clonazepam 0.5 mg i.v. for further twitching and at 48 h she had tonic clonic spasms affecting the legs more than the arms. Each episode lasted for about 1 min, with associated cyanosis, and eventually she had a grand mal seizure. The airway was maintained, oxygen therapy was continued and additional clonazepam 2 mg i.v. was given in increments. Pethidine was discontinued and carbamazepine, which had been omitted for the previous 4 days, was recommenced. The patient was transferred to the Intensive Care Unit. No further grand mal seizures occurred, but twitching and muscle spasms were noted for another 5 days. The patient made a full neurological recovery.

During the 9 days preceding laparotomy, she had received pethidine up to 375 mg day^{-1}. After the laparotomy, she was given pethidine PCA with 10-mg boluses but no background infusion. Because of lack of pain control, boluses were increased to 20 mg on the first day after operation. The patient had self-administered pethidine 1760 mg and 1540 mg in the first and second 24-h periods, respectively.

The blood concentration of norpethidine on the day after the convulsion was 1.55 μg ml^{-1}.

On the day of the convulsion, serum potassium concentration was 2.6 mmol litre^{-1} and creatinine concentration 0.12 μmol litre^{-1}. Serum ionized calcium was normal, blood glucose was 13.5 mmol litre^{-1} and serum concentration of theophylline was not in the toxic range. Arterial blood–gas tensions with oxygen therapy via a face mask immediately after treatment of the convulsion were $P\text{O}_2$ 8 kPa, $P\text{CO}_2$ 8 kPa and pH 7.24. This respiratory acidosis and relative hypoxia resolved with oxygen therapy and spontaneous ventilation.

Patient No. 2

A 21-yr-old, 51-kg female was admitted for an abdomino–perineal resection of the rectum for Crohn's disease. She was suspected of opioid abuse. On admission to hospital, she reported that she had not taken pethidine recently. There was no history of convulsions. Her drug therapy was oral prednisolone, azathiaprine and metronidazole. She claimed to have a morphine "allergy", which caused hallucinations.

She received pethidine 200–400 mg i.m. for perineal inflammatory pain daily for 5 days before operation. After operation, i.v. pethidine by PCA was commenced, with 10-mg boluses and 10 mg h^{-1} by background infusion. The bolus size was increased to 20 mg 12 h later, as analgesia was considered to be uncontrolled. On the second day after operation, the patient had myoclonic jerks and felt frightened. She had used an average of pethidine 1240 mg/24 h. Norpethidine toxicity was suspected, pethidine was discontinued and morphine commenced by PCA. The myoclonic twitching abated with this regimen.

This patient's blood norpethidine and pethidine concentrations shortly after ceasing pethidine were

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Table I. *Pethidine doses used by the three patients receiving PCA*

	Patient 1	Patient 2	Patient 3
1st 24 h (mg)	1760	1200	1200
Next 20.5 h (mg)		1100	
or 2nd 24 h (mg)	1540		1280
Next 2 h (mg)	200		
or 4 h (mg)			280
Average dose in 24 h (mg)	1344	1240	1274
(mg/kg b. wt)	24.9	24.3	24.0

Table II. *Doses of pethidine received during 24 h on PCA, timing of blood samples after stopping pethidine and blood concentrations of norpethidine (Norpeth.) and pethidine (Peth.) where available*

	Pethidine (mg)			Blood concn (µg ml^{-1})	
Patient No.	Before PCA	Average/24 h PCA	Time to sample (h)	Norpeth.	Peth.
1	1900 in 9 days	1680	18	1.55	—
2	1700 in 5 days	1240	1	3.2	1.7
3	0	1274	1	1.67	2.4

3.2 and 1.7 µg ml^{-1}, respectively. Serum urea, electrolytes, creatinine and blood glucose concentrations were normal.

Patient No. 3

A 31-yr-old, 53-kg female with a 4-yr history of Crohn's disease was admitted to hospital with small bowel obstruction. Four days later, she required laparotomy and right hemicolectomy. Before admission, loperamide was her only drug therapy. No pethidine was given before operation.

After operation, the patient was given i.v. pethidine by PCA. Bolus doses were increased from 10 mg to 20 mg because of lack of pain control after 2.5 h. There was no background infusion.

On the first day after operation, she was noted to be anxious and to have a strange affect. She had consistently reported high pain scores, despite having used pethidine 1200 mg in 24 h. She did not feel tremorous and had no involuntary movements. PCA pethidine was continued and on the second day after operation she seemed more agitated and reported that she felt frightened. She had used pethidine 1280 mg in the second 24 h. The pain scoring had remained high.

Pethidine was stopped and morphine PCA started. The patient received three 5-mg i.v. doses of diazepam over the next 24 h. She felt less frightened and her pain scores improved. She used morphine 106 mg over the next 24-h period.

The blood norpethidine and pethidine concentrations were 1.67 and 2.4 µg ml^{-1}, respectively, shortly after cessation of pethidine. Serum urea, electrolytes, creatinine and blood glucose concentrations were normal.

Pethidine dosage and blood concentrations

The amounts of pethidine used by these three patients while receiving PCA, including their average 24-h dosage, are shown in table I. The amount of pethidine administered to each patient, the time between stopping pethidine and sampling for blood concentrations and the blood concentrations of norpethidine (and pethidine where available) are summarized in table II.

DISCUSSION

Pethidine is metabolized by two hepatic pathways, hydrolysis and N-demethylation, to pethidinic acid and norphethidine, respectively. Norpethidine is hydrolysed similarly to an acidic form. Urinary excretion is the principal elimination route. The elimination half-life of pethidine is 3–6 h, whilst that of norpethidine is at least 15 h, and up to 35 h in patients with renal failure [1, 2].

Norpethidine has CNS excitatory effects in animals and there is evidence [3] of increasing intensity of CNS excitation correlating with accumulation of norpethidine in plasma in human subjects receiving pethidine. The excitatory effects range from mild nervousness through tremors, twitches and multifocal myoclonus to seizures.

Norpethidine toxicity has been described well in various clinical situations [3–10]. Reduced renal function has been noted to predispose to accumulation of norpethidine [1, 11]. Goetting, Thirman and Arbor [5] described norpethidine neurotoxicity in a patient self-administering oral pethidine after operation. Oral pethidine predisposes to norpethidine toxicity because of extensive first-pass hepatic metabolism.

These are the first reported cases of norpethidine toxicity in association with parenteral PCA pethidine. In our first two patients there had been some administration of pethidine before starting PCA. This would have provided an opportunity for both cumulation of norpethidine before operation and the development of tolerance to the analgesic effect of pethidine. The latter would predispose to an early increased use of PCA pethidine for analgesia. In addition, some enzyme induction from previous drug administration could have predisposed to N-demethylation. In the third patient, the only preoperative drug therapy was loperamide. Loperamide, a piperidine derivative, is a congener of pethidine and its metabolism in the rat includes oxidative-N-demethylation [12]. Oral loperamide is partly excreted unchanged in the faeces (25–40 % in man) and it does not exert opioid activity in normal therapeutic doses [13]. We suggest that there may have been potential for induction of N-demethylation enzymes related to chronic administration of loperamide in our third patient. This could have predisposed to the development of norpethidine toxicity with PCA pethidine.

The blood concentrations of norpethidine (assayed by a chromatographic method) in our patients (table I) were within and greater than the ranges of plasma concentrations of norpethidine associated with CNS excitation observed by Kaiko and colleagues [3]. Edwards and colleagues [11] found in several studies that blood and plasma concentrations of pethidine are comparable and therefore it seems reasonable to compare our results from blood with plasma concentrations described elsewhere. For the two patients in whom the blood norpethidine:pethidine ratio was available, it was within the ranges associated with evidence of CNS excitation in the study by Kaiko's group [3].

Previous case reports have suggested that, if long-term or high-dose opioid analgesia is anticipated, especially in the presence of renal impairment, the use of pethidine may carry an appreciable risk of norpethidine toxicity. We suggest that use of pethidine immediately before surgery may also predispose to increased risk of developing norpethidine toxicity if pethidine is to be used after operation. This risk is increased in a situation in which the patient may receive large doses of pethidine, as with PCA. In all three patients, analgesia was poor and this exacerbated the tendency to administer more pethidine.

Any patient receiving pethidine in repeat doses should be monitored for early signs of norpethidine toxicity. If norpethidine toxicity is suspected, pethidine should be ceased, and ventilatory support and anticonvulsant therapy given if indicated. Naloxone does not reverse norpethidine toxicity and may worsen the situation by its antagonistic effect on the CNS-depressant effect of pethidine [14]. Morphine is usually a suitable substitute analgesic as it lacks a major excitatory metabolite such as norpethidine. However, it should be noted that morphine may exhibit some neuroexcitatory effects in very large doses [2, 15].

All three of our patients were using pethidine in excess of 1200 mg/24 h on PCA, equivalent to 24–25 mg kg^{-1}/24 h. The results of a recent study of norpethidine toxicity in sickle cell crisis [10] suggested that daily doses of parenteral pethidine exceeding 25 mg kg^{-1} may be associated with toxicity, especially in the presence of renal impairment or if pethidine had been taken orally before hospital admission.

Our first patient had appeared to be anxious and patients Nos 2 and 3 had volunteered that they felt frightened, in association with the use of more than 1200 mg of pethidine in 24 h and apparent poor quality of analgesia. The presence of anxiety in patients receiving large doses of pethidine without the expected analgesic response should alert to the possibility of norpethidine toxicity.

Approximately 10 % of the 1500 patients each year who use postoperative PCA within the Acute Pain Service at the Royal Adelaide Hospital are prescribed pethidine. Morphine is the preferred drug. Those receiving pethidine usually do so because of a history of morphine allergy or a stated preference by the patient in light of previous experience. The majority of patients who have been given PCA pethidine experienced no problems. Our three patients presented in the same hospital over a 2-year period and are presented in chronological order.

Our patients demonstrate that, although PCA is generally considered to be safe in terms of ventilatory and sedative side effects in healthy patients, this complication of metabolite toxicity can develop. In addition to monitoring ventilation and state of sedation, frequent clinical assessment and recording the amount of drug used is required to minimize such risks.

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APPARATUS

EFFICIENCY OF BREATHING SYSTEMS A AND D IN THE CARDEN VENTMASTA VENTILATOR

E. J. THAM, R. DAVIES, J. M. SLADE AND W. W. MAPLESON

SUMMARY

We have compared the efficiency of the enclosed Magill attachment (System A) and the co-axial System D (Bain) in the Carden Ventmasta ventilator using both systems, each under five different ventilatory conditions, in each of five anaesthetized patients. Efficiency was assessed in terms of the effective alveolar ventilation as a fraction of the fresh gas flow. For System A, efficiency increased from a mean of 0.37 when the total ventilation was only 50% of the fresh gas flow, to a mean of 0.74 when ventilation was 2.3 times the fresh gas flow. The efficiency was substantially and significantly less with System D: 75% of that for System A at the smaller total ventilation (95% CI 65–85%) and 65% at the larger (95% CI 59–71%). A critical examination is made of conflicting definitions and terminology of the efficiency of breathing systems. (Br. J. Anaesth. 1993; **71**: 741–746).

KEY WORDS

Equipment: breathing systems, Magill attachment, Bain system, Carden Ventmasta. Ventilation: efficiency.

Of the five anaesthetic breathing systems analysed by Mapleson [1], the Magill attachment (System A) is more efficient than System D in spontaneous ventilation [1], but it becomes inefficient in controlled ventilation [2] because the spill valve opens during the inspiratory phase instead of towards the end of the expiratory phase. However, if the spill valve is held closed during the inspiratory phase and left free to open during the expiratory phase, as in the "Enclosed" System A [3, 4] it can be expected [3] that the system may regain the efficiency that it has in spontaneous ventilation and so be more efficient than System D.

A group of investigators from Manchester [5] studied the enclosed System A developed by Ohmeda and supplied with their 7800 ventilator. They measured the efficiency of the system during controlled ventilation in 10, mostly elderly, patients and over a wide range of ratios of total ventilation to fresh gas flow. They compared their results with those obtained by Rose and Froese in 1979 [6] for the Bain system during controlled ventilation in children and stated that the efficiency of the Ohmeda enclosed System A was "similar to that obtained with a Bain system" (a coaxial System D). This was surprising, especially as Criswell and colleagues [7] had shown already that, under typical conditions of controlled ventilation, end-tidal concentrations were significantly smaller with an enclosed System A than with the Bain system. This discrepancy prompted the present study.

Some models of the Engström MIE Carden Ventmasta ventilator provide the facility to switch between System D and the enclosed System A. We therefore compared the two systems by using them alternately on each of a number of anaesthetized patients.

During the conduct of our study, the Manchester group of investigators revised their conclusions about the efficiency of the Ohmeda enclosed System A [8, 9], but we believe that the present direct comparison of the enclosed System A with System D in a different ventilator is nevertheless of interest.

METHODS

General approach

In spontaneous ventilation, the relative merits of breathing systems are expressed commonly in terms of how large the fresh gas flow should be (as a multiple or fraction of the total or alveolar ventilation) in order to eliminate rebreathing. The same approach can be used in controlled ventilation if the total ventilation is decided first. However, there is much to commend the approach, implicit in the study by Snowdon and colleagues [10], of first choosing a fresh gas flow and then setting a total ventilation which is sufficient to ensure that an adequate fraction of that fresh gas flow reaches the alveoli, to be converted to alveolar gas. The rate at which fresh gas is so converted we term the "effective alveolar ventilation" ($\dot{V}_A^{eff}$). This is to distinguish it from plain "alveolar ventilation" ($\dot{V}_A$), which is often defined as frequency times (tidal volume minus deadspace), and which may include some alveolar gas rebreathed from the breathing system. The rate

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TABLE I. *The 10 ventilatory conditions (all with a frequency of 12 b.p.m. and an* I:E *ratio of 1:2)*

Enclosed System A		System D	
Fresh gas flow (litre min^{-1})	Tidal volume (ml)	Fresh gas flow (litre min^{-1})	Tidal volume (ml)
9.4	400	9.4	440
5.8	330	6.7	410
4.2	440	5.2	560
3.9	580	4.7	710
3.9	780	4.3	870

of elimination of carbon dioxide ($\dot{V}\text{CO}_2$), is that fraction of the effective alveolar ventilation which contains carbon dioxide:

$$\dot{V}\text{CO}_2 = F\text{A}_{\text{CO}_2} \times \dot{V}\text{A}^{\text{eff}}$$

where $F\text{A}_{\text{CO}_2}$ = mean alveolar carbon dioxide concentration. We followed Snowdon and colleagues [10] in using end-tidal carbon dioxide concentration ($F\text{E}'_{\text{CO}_2}$) as an indication of $F\text{A}_{\text{CO}_2}$. It is, in fact, the flow-weighted mean of the concentrations in the alveoli. Therefore we calculated the effective alveolar ventilation from:

$$\dot{V}\text{A}^{\text{eff}} = \dot{V}\text{CO}_2/F\text{E}'_{\text{CO}_2}$$

In an ideal system, a "maximum efficiency system", all the fresh gas would be used in providing alveolar ventilation. In any real breathing system, only a fraction of the fresh gas is used; the remainder escapes, unaltered, through the spill valve. Efficiency can then be defined as $\dot{V}\text{A}^{\text{eff}}/\dot{V}\text{F}$, where $\dot{V}\text{F}$ = fresh gas flow. Efficiency generally increases as the total ventilation ($\dot{V}\text{E}$) increases relative to the fresh gas flow. We have therefore followed Snowdon and colleagues in presenting our results in terms of a plot of efficiency ($\dot{V}\text{A}^{\text{eff}}/\dot{V}\text{F}$) against $\dot{V}\text{E}/\dot{V}\text{F}$. A full discussion of conflicting definitions and terminology of the efficiency of breathing systems is given in the Appendix.

Patients

The inclusion criteria for patients were: age 18–65 yr; weight 45–90 kg; ASA I or II; free of respiratory disease; scheduled to undergo elective surgery expected to last at least 3 h. We excluded patients for neurosurgery or thoracotomy, those receiving a carbon dioxide pneumoperitoneum or sodium bicarbonate and patients for whom any of the planned ventilatory conditions would be inappropriate. Five patients were studied; all gave informed consent. The study was approved by the local Ethics Committee.

Experimental design

All ventilation was performed at 12 b.p.m. with an I:E ratio of 1:2. Five different $\dot{V}\text{E}/\dot{V}\text{F}$ values were used with each system giving a total of 10 different ventilatory conditions. The actual values of $\dot{V}\text{E}$ and $\dot{V}\text{F}$ (table I) were somewhat different for the two systems: they were chosen on the basis of preliminary laboratory tests with a model lung and were intended to produce $\dot{V}\text{E}/\dot{V}\text{F}$ values of approximately 0.5, 0.7, 1.3, 1.8 and 2.4 with both systems and an alveolar ventilation of approximately 3 litre min^{-1} with all 10 conditions.

A computer-generated randomization sequence was used to determine which breathing system and which ratio should be used first in each patient. This was followed by the other system with the same $\dot{V}\text{E}/\dot{V}\text{F}$ value. Subsequently, each system was used in turn at each of the other four ratios. The ratios were used in sequence, working up to the greatest and then, where necessary, restarting at the smallest until all 10 ventilatory conditions had been applied. With each condition, the required measurements were made after at least 13 min in that condition and in a pseudo steady state ($F\text{E}'_{\text{CO}_2}$ before and after the 2-min measurement period agreeing to within 0.05 kPa).

The Ventmasta was serviced by the manufacturer immediately before the study and was used exclusively for this study.

Measurements

The fresh gas flow was read from the Rotameters on the anaesthetic machine, which were calibrated against a dry gas meter. Total ventilation was determined from tidal volume and frequency. Tidal volume was measured with a Magtrak electrical turbine-spirometer; frequency (12 b.p.m.) and I:E ratio (1:2) were set by including a pneumotachograph in the inspiratory limb of the breathing system and displaying the output on a paper chart recorder. The frequency was verified periodically by counting and timing.

$F\text{E}'_{\text{CO}_2}$ was measured by a Datex Normocap infrared analyser sampling from the tracheal tube connector at 150 ml min^{-1}. Carbon dioxide elimination was determined as follows. All gas emerging from the exhaust port of the ventilator was collected for 2 min into an airtight bag. The volume of gas collected ($V\text{bag}$) was measured by expelling the contents of the bag through a Parkinson Cowan dry gas meter. The carbon dioxide concentration in the gas ($F\text{bag}_{\text{CO}_2}$) was measured by requiring the Datex Normocap to obtain a continuous sample from a point in the expelled gas stream between the bag and the dry gas meter and returning it to another point, downstream. The rate of elimination of carbon dioxide from the ventilator was calculated from

$$\dot{V}\text{CO}_2 = F\text{bag}_{\text{CO}_2} \times V\text{bag}/t$$

where t = duration of collection. As all carbon dioxide originated in the patient and the end-tidal carbon dioxide concentration was stable during the collection period, $\dot{V}\text{CO}_2$ was also the rate of elimination of carbon dioxide from the pulmonary circulation.

Procedure

All patients were premedicated with temazepam 20 mg orally, 1 h before surgery. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 1–2 µg kg^{-1}; vecuronium 0.1 mg kg^{-1} was given to facilitate tracheal intubation. Anaesthesia was main-

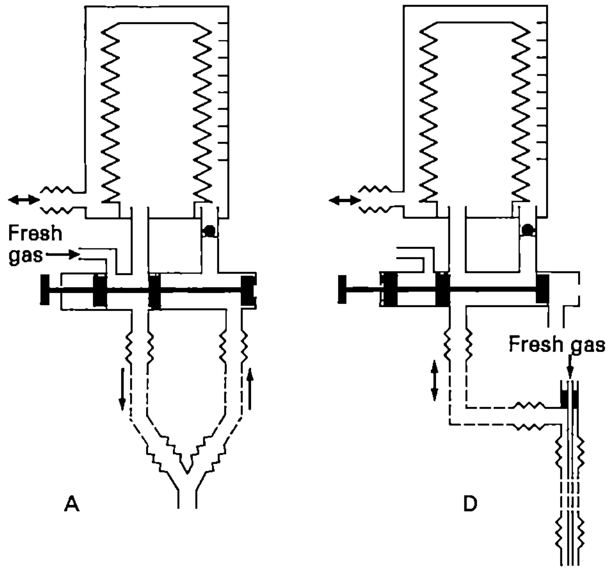

FIG. 1. The output portion of the Carden Ventmasta with the enclosed A and coaxial D (Bain) breathing systems.

tained with enflurane and 50–66 % nitrous oxide in oxygen, supplemented with fentanyl as required. Incremental doses of vecuronium 0.01 mg kg^{-1} were given to maintain neuromuscular block, which was monitored by tactile observation of the response to a train of four supramaximal stimuli. Electrocardiogram, arterial pressure, arterial saturation by pulse oximetry and $F\mathrm{E}'_{\mathrm{CO_2}}$ were monitored throughout the procedure.

Patients were connected to the Carden Ventmasta using twin corrugated tubes for the enclosed System A and a Bain system for the (coaxial) System D (fig. 1). A heat and moisture exchanger (Pall filter) and the Magtrak turbine were placed in series with the catheter mount. The total geometric deadspace was 120 ml, total resistance 0.3 kPa litre^{-1} s at 1 litre s^{-1}. During the first 10 min with each ventilatory condition, the tidal volume was sometimes adjusted to avoid extremes of $F\mathrm{E}'_{\mathrm{CO_2}}$. All gas flows and volumes were corrected to ATPS for consistency.

Statistical analysis

Curve fitting was with the statistical package GLIM [11, 12], release 3.77, running on a DEC mainframe computer running under the Ultrix operating system (V4.0).

RESULTS

The characteristics of the five patients studied are listed in table II. The exigencies of the clinical circumstances led to occasional deviations from the planned sequence of ventilatory conditions, but all 10 conditions were applied in all patients except one: with patient No. 2, concern over the reliability of some of the measurements led us to use only the smallest, largest and middle ventilation with each system, but to use them all twice. The small SD between these replicate measurements (0.014 efficiency) showed that our concern was unnecessary.

The calculated efficiency ($\dot{V}\mathrm{A}^{\mathrm{eff}}/\dot{V}\mathrm{F}$) is plotted against total ventilation as a multiple of fresh gas

TABLE II. *Characteristics of the patients in the study*

Patient No.	Age (yr)	Weight (kg)	Sex	ASA grade	Operation
1	49	76	F	I	Isolated limb perfusion
2	31	48	F	I	Breast reconstruction
3	64	69	F	II	Isolated limb perfusion
4	61	82	M	II	Anterior resection of bowel
5	60	71	F	II	Breast reconstruction
Mean	53	69.2	—	—	—

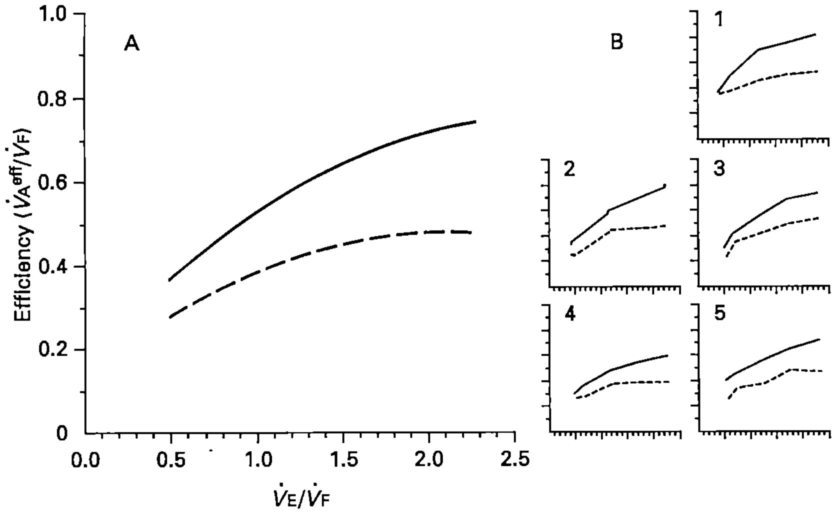

FIG. 2. Efficiency (effective alveolar ventilation ($\dot{V}\mathrm{A}^{\mathrm{eff}}$) as a fraction of fresh gas flow ($\dot{V}\mathrm{F}$)) plotted against total ventilation ($\dot{V}\mathrm{E}$) as a multiple of fresh gas flow ($\dot{V}\mathrm{F}$) for the enclosed Magill attachment (enclosed System A) and the coaxial System D (Bain) in the Carden Ventmasta ventilator in patients whose lungs were ventilated at a frequency of 12 b.p.m. and an I:E ratio of 1:2 through a Pall filter and Magtrak turbine (total geometric deadspace 120 ml) and a tracheal tube. $\dot{V}\mathrm{A}^{\mathrm{eff}}$ calculation base on $F\mathrm{E}'_{\mathrm{CO_2}}$; all flows and ventilations at ATPS. A: Two parabolas fitted to all the data for each system. B: Miniature versions of the same plot for the individual measurements in the five patients.

TABLE III. *Efficiency* ($\dot{V}A^{eff}/\dot{V}F$) *of System D as a percentage of that of the enclosed System A at different values of* $\dot{V}E/\dot{V}F$ *within the range of measurements corrected to* ATPS *(means and confidence intervals for five patients)*

	Efficiency D/Efficiency A (%)		
$\dot{V}E/\dot{V}F$	Mean	95 % CI	99 % CI
0.5	75.3	65.3–85.3	58.7–91.9
1.0	73.0	69.6–76.4	67.4–78.6
1.5	70.6	66.6–74.5	64.0–77.1
2.0	67.5	63.1–71.8	60.3–74.6
2.3	65.2	59.1–71.3	55.1–75.3

flow ($\dot{V}E/\dot{V}F$) in figure 2A (two parabolas fitted to all the data for each system (maximum efficiency for system A, 0.74)) and B (miniature versions of the same plot for the individual measurements in each of the five patients). These graphs show that System D was substantially less efficient than System A in these five patients: in terms of the parabolas, System D had 75 % of the efficiency of System A when the total ventilation was 50 % of the fresh gas flow, decreasing to 65 % when the ventilation was 2.3 times the fresh gas flow. In terms of the miniature graphs, this general pattern appeared to be broadly consistent for all five patients.

To assess this consistency, it was necessary to determine the differences between Systems A and D at fixed values of $\dot{V}E/\dot{V}F$. As the observations were not made at exactly the same values of $\dot{V}E/\dot{V}F$, a separate parabola was fitted to the results for each patient on each system. (These gave a close fit, with an overall residual SD of only 0.021 efficiency.) Then, for each patient, efficiency was calculated from the individual D parabola and expressed as a percentage of that calculated from the corresponding A parabola; this was done for five values of $\dot{V}E/\dot{V}F$. The resulting mean percentages were similar to those derived from the parabolas shown in figure 2 and the confidence limits on the percentages were close at the intermediate values of $\dot{V}E/\dot{V}F$ (table III). The use of a cross-over experimental design enabled us to obtain a clear result with only a few patients. However, 99 % confidence limits in addition to the usual 95 % limits are given in the table because the former widen more rapidly than the latter as the number of degrees of freedom decreases: at four degrees of freedom (as here) the 99 % confidence interval is 1.66 times the 95 % interval, compared with 1.33 times at 60 degrees of freedom.

DISCUSSION

Performance

It is clear from figure 2 and table III that the Carden Ventmasta implementation of the enclosed System A was considerably more efficient than the coaxial System D (Bain)—contrary to the original expectation of the Manchester group [5]. However, we were surprised that the maximum efficiency of the enclosed A was only 74 % (at $\dot{V}E/\dot{V}F = 2.3$). This is similar to the maximum of 73 % reported originally by the Manchester group [5] for the Ohmeda enclosed System A in adults but, as the group has now acknowledged [8, 9], this value was achieved because they were using the arterial concentration of carbon dioxide (Pa_{CO_2}) instead of PE'_{CO_2} in calculating the efficiency of the breathing system—thereby including the considerable inefficiency (in their elderly patients) of gas exchange between gas and blood. When they recalculated their results in terms of PE'_{CO_2} [9], the maximum efficiency became 88 %.

The likely reason for the low efficiency of the enclosed System A in the present study was revealed by recordings made in the laboratory, with the Ventmasta connected to a passive model lung. These showed a brief period of flow along the expiratory limb of the breathing system (fig. 1) at the very beginning of the expiratory phase. Thereafter, flow in that limb did not recommence until the inflating bellows had re-expanded fully. Therefore, some of the fresh gas from the deadspace of the patient (which gas, in spontaneous ventilation, would have gone into the inspiratory limb towards the bellows) was not conserved in the way that is necessary for high efficiency.

This premature opening of the ball valve could not be explained in terms of the pressure difference attributable to the resistance of the inspiratory limb or to the static compliance of the bellows. However, plotting pressure difference between the Y-piece and the outside of the bellows against flow into the bellows showed much larger pressure differences than were accounted for by the resistance of the tubing from Y-piece to bellows plus the static pressure–volume characteristic of the bellows. These pressure differences during the high peak flows early in expiration are sufficient to open the ball valve.

Thus, in addition to their compliance, the bellows seem to have some dynamic resistance to expansion. This may arise from the oil-like film with which the folds of the bellows are coated. This is intended to prevent the folds sticking together during storage; however, it seems that the surface tension of this oil hinders the separation of the folds as the bellows expand. The manufacturer is addressing this problem.

Application of the results

The arrangement of figure 2 is useful for comparing the efficiencies of different systems, but not very convenient for working out the clinical implications of using a particular system. For example, suppose it is desired to achieve an alveolar ventilation of 3 litre min^{-1} with a minimum usage of fresh gas. Within the range of figure 2, this could be done best with System A (using the parabola fitted to all the System A results) by attempting to achieve an efficiency of 0.74. This would require a fresh gas flow of $3/0.74 = 4.1$ litre min^{-1} which, in turn, would require a total ventilation of 2.3 times the fresh gas flow, or 9.4 litre min^{-1}. Alternatively, if the same alveolar ventilation were desired, but with a minimum of total ventilation, an efficiency of only 0.37 could be accepted, requiring a fresh gas flow of $3/0.37 = 8.1$ litre min^{-1} and a $\dot{V}E/\dot{V}F$ value of 0.5 and hence a total ventilation of 4.0 litre min^{-1}.

The requisite information is presented in a more convenient form in figure 3, where the equation to

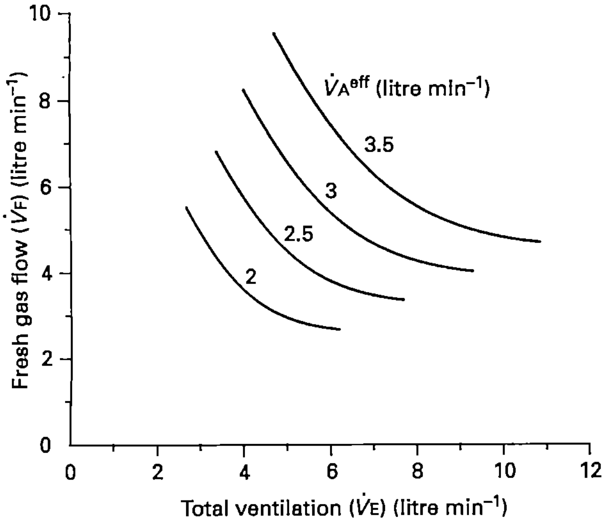

FIG. 3. Relationship of the parabola for System A in figure 2A replotted in terms of required fresh gas flow against required total ventilation for various values of effective alveolar ventilation ($\dot{V}\mathrm{A}^{\mathrm{eff}}$). The curves are limited to the ranges of values of $\dot{V}\mathrm{A}^{\mathrm{eff}}$ and $\dot{V}\mathrm{E}/\dot{V}\mathrm{F}$ encountered in the measurements. (Note the circumstances in which the data were obtained—see caption to figure 2.)

the System A parabola in figure 2 has been used to plot $\dot{V}\mathrm{F}$ against $\dot{V}\mathrm{E}$ for each of a number of values of alveolar ventilation. Thus the user can select the desired alveolar ventilation and, then, either choose a particular fresh gas flow and read off the necessary total ventilation, or choose a particular total ventilation and read off the necessary fresh gas flow. In using this graph, or those in figure 2, however, it must be remembered that the curves relate to the mean of the five patients studied when their lungs were ventilated through a Pall filter and Magtrak turbine (total geometric deadspace 120 ml) and a tracheal tube, at a frequency of 12 b.p.m., an I:E ratio of 1:2 and using a particular Carden Ventmasta.

APPENDIX

DEFINITIONS AND TERMINOLOGY OF EFFICIENCY OF BREATHING SYSTEMS

Definitions

In general scientific usage, the meaning of "efficiency" is the fraction or percentage of an input (of energy or material) which is used for the intended purpose, the remainder being wasted. In terms of breathing systems, the intended purpose of the fresh gas is for it to be delivered to the lungs and take part in gas exchange. Therefore, in the steady state, the gas which is vented from the system may be regarded as a mixture of wasted (unchanged) fresh gas ($F\mathrm{F}$) and "used" gas ($F\mathrm{U}$). Thus, if f = fractional efficiency and $F\bar{\dot{\mathrm{V}}}_x$ = mean concentration of a chosen component, x, in the vented gas:

$$F\bar{\dot{\mathrm{V}}}_x = fF\mathrm{U}_x + (1-f)F\mathrm{F}_x$$

Therefore:

$$f = \frac{F\bar{\dot{\mathrm{V}}}_x - F\mathrm{F}_x}{F\mathrm{U}_x - F\mathrm{F}_x} \qquad (1)$$

Thus defined, efficiency can be determined from any component of respired gas; in the case of carbon dioxide, or any other gas which is absent from fresh gas, equation (1) may be simplified to:

$$f = F\bar{\dot{\mathrm{V}}}_x / F\mathrm{U}_x \qquad (2)$$

Whichever equation is used, the result obtained depends on what value is used for $F\mathrm{U}_x$—that is, what is regarded as "used" gas. (In the Ventmasta, vented gas is immediately mixed with the driving gas of the ventilator so we had to use a more indirect approach, but this can be shown to be essentially equivalent to equation (2).)

One extreme is to define as "used" any gas which enters the patient's respiratory system, in which case $F\mathrm{U}_x$ will become $F\mathrm{E}_x$, the mixed-expired concentration. This was implicit in Fitton's mathematical definition of a "maximal efficiency system" in a theoretical study of inspired oxygen concentrations in 1958 [13, 14]; this was probably the first use of the term "efficiency" in relation to breathing systems. However, with this definition of "used", in a system in which end-tidal gas is vented preferentially (such as System A in spontaneous ventilation and the enclosed A in controlled ventilation), the vented concentration ($F\bar{\dot{\mathrm{V}}}_x$) approximates to the end-tidal concentration ($F\mathrm{E}'_x$) and the calculated efficiency is greater than 100%. We do not find this an attractive approach.

The other extreme is that adopted by Rose and Froese in 1979 [6], and followed originally by the Manchester group [5], of setting $F\mathrm{U}_x$ equal to $F\mathrm{a}_x$, where $F\mathrm{a}_x$ must be understood to mean the fractional concentration of x with which arterial blood would be in equilibrium. As noted in the introduction, the Manchester group later acknowledged [8, 9] that this includes, in f, the inefficiency of gas exchange in the lungs and this can never be compensated for by the breathing system.

The intermediate approach is to set $F\mathrm{U}_x$ equal to the end-tidal concentration ($F\mathrm{E}'_x$)—the flow-weighted mean of $F\mathrm{A}_x$. This was done by Snowdon [10], who seems to have been the first to measure the efficiency of a breathing system (in 1975) and also by Conway [15] in his theoretical analysis in 1976. Ideally [1], this could result in 100% efficiency in System A without any rebreathing. In practice, there is always some mixing of end-tidal gas and fresh gas from the deadspace, both in the lungs and in the breathing system. However, if the total ventilation is made sufficiently greater than the fresh gas flow, the "plug" of mixed end-tidal and deadspace gas which enters the breathing system during the expiratory phase could all be driven back into the alveoli in the next inspiratory phase. Then, only end-tidal gas would be vented. Therefore, 100% does represent a theoretical limit to the efficiency of the enclosed System A, if the end-tidal concentration is regarded as the "used" concentration—although the degree of hyperventilation required might be unacceptable or even impractical.

A definition of efficiency which gives 100% as a just, or not quite, attainable upper limit seems ideal and we therefore recommend the use of end-tidal concentration as the "used" concentration in the determination of the efficiency of anaesthetic breathing systems.

It is worth noting also that, ideally, efficiency based on end-tidal concentration is not affected by changes in parallel deadspace. Thus, consider a given ventilation, fresh gas flow and carbon dioxide elimination rate: if parallel deadspace increases, the concentration in the perfused alveoli must increase to an extent such that the mixed alveolar (end-tidal) concentration remains the same, in order to maintain the same rate of elimination of carbon dioxide. Also, if System A behaved ideally (efficiency = 1 for $\dot{V}\mathrm{E}/\dot{V}\mathrm{F} > V\mathrm{T}/(V\mathrm{T} - V\mathrm{D})$), the only effect of a change in series deadspace would be to change the value of $\dot{V}\mathrm{E}/\dot{V}\mathrm{F}$ at which efficiency began to decrease to less than unity. However, as the efficiency of the present System A never achieved unity, it must be allowed that a different series deadspace could lead to a different efficiency. Similarly, some theoretical calculations by one of us (W.W.M.), based on Dorrington's geometrical construction [16, 17], suggest that the size of series deadspace has some effect on the efficiency of System D. Finally, if perfused and unperfused alveoli empty with unequal time constants, the flow weighting changes during the expiratory phase and the "plateau" of carbon dioxide concentration in the later part of expiration is sloped; then end-tidal concentration is not a *mean* flow-weighted mean of alveolar concentration. This did not occur in our patients.

Terminology

The pioneers just used "efficiency", based on mixed-expired (Fitton [13, 14]) or end-tidal (Snowdon [10]) concentration, or simply "f" (Conway [15]), based on "alveolar" concentration which, in the context, would be mixed alveolar or end-tidal concentration. Rose and Froese [6] introduced the term "fractional utilization" of fresh gas for efficiency calculated by using arterial carbon dioxide ($F\mathrm{a}_{\mathrm{CO_2}}$) in 1979. The Manchester group initially followed this usage [5, 8], but recently [9] introduced the term "fractional delivery" for efficiency calculated by using end-tidal concentration.

We consider that "fractional delivery" is a good term for efficiency based on end-tidal concentration—first, because it represents that fraction of the fresh gas which is delivered to the gas-exchanging part of the lungs (for the lungs to use as best they can) and second, because the maximum that can be "delivered" is 100%—the same as the maximum for efficiency defined in this way.

We are therefore disappointed in a draft European Standard on "Anaesthetic Workstations and Their Modules" [18] because this incorporates a test for "fresh gas utilization" in controlled ventilation which includes the statement "The fresh gas utilization expresses the fraction of fresh gas reaching the patient's lung". This raises the question how far into the patient's respiratory tract does "the lung" begin? If it be taken to begin at the Y-piece of the breathing system, it would be appropriate to use mixed-expired concentration as representing "used" gas (with all the disadvantages given above); but if "the lung" be taken to mean gas-exchanging part of the lung, end-tidal concentration should be used. In fact, the test apparatus incorporates a model lung which absorbs a tracer gas present in the fresh gas. Efficiency is calculated from equation (1) by measuring $F\mathrm{F}_x$ and $F\dot{\mathrm{V}}_x$, and assuming that $F\mathrm{U}_x$ is zero, implying total absorption—and therefore that $F\mathrm{U}_x = F\mathrm{E}'_x$.

Thus the "fresh gas utilization" of the draft European Standard appears to be the same as the Manchester group's "fractional delivery" (and the same as efficiency as calculated in the present paper)—except that the model lung of the draft Standard has a series deadspace of only 50 ml. Therefore, the enclosed System A is still able to approach 100% efficiency; whereas in systems in which some fresh gas is always wasted, such as System D, the measured efficiency may differ from that in a real patient with a deadspace of substantially more than 50 ml. This may therefore affect the order of merit of the eight circle systems tested by Zbinden, Feigenwinter and Hutmacher [19] using the method specified in the draft Standard.

In passing, it is worth noting that, although the Manchester group refer to the Ohmeda breathing system as an "enclosed afferent reservoir system", it is specifically an enclosed System A. "Afferent reservoir" systems also include [20] Systems B and C as originally drawn by Mapleson [1], although they may be converted to efferent reservoir systems by exchanging the positions of the fresh gas inlet and spill valve [20].

ACKNOWLEDGEMENT

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CONTINUOUS SPIROMETRY: AN AID TO MONITORING VENTILATION DURING OPERATION

G. I. BARDOCZKY, E. ENGELMAN AND A. D'HOLLANDER

SUMMARY

We present six case-reports of patients who experienced inadequate ventilation as a result of endobronchial or oesophageal intubation, or obstruction to the tracheal tube or airway and were monitored with on-line spirometry. The continuously displayed pressure–volume or flow–volume loops may be compared with previously recorded baseline loops. The changing configuration of the curves offers additional and instantaneous information about the cause of increased inspiratory airway pressure, decreased compliance or increased airway resistance. Monitoring flow–volume and pressure–volume loops in conjunction with currently available techniques provides a comprehensive method of monitoring ventilation. (Br. J. Anaesth. 1993; **71**: 747–751)

KEY WORDS

Intubation: complications. Monitoring: spirometry, flow–volume loop, pressure–volume loop.

Routine intraoperative monitoring of the respiratory system includes tidal volume, inspiratory airway pressure and inspiratory and expiratory gas concentrations. With the development of new, microprocessor-based sensor technology, in-line spirometry is incorporated into some monitors, allowing closer evaluation of respiratory physiology during operation.

The Ultima SV respiratory monitor (Datex Instrumentarium Corp. Helsinki, Finland) is used for routine intraoperative monitoring in our department. An integral part of the monitor comprises spirometry by a newly developed flow sensor and respiratory gas sampling probe [1]. The flow sensor is placed between the Y-piece and the tracheal tube of the breathing system. It is a bi-directional, pressure-based flow sensor, with two fixed resistances interposed in the airflow (fig. 1). The pressure difference caused by gas flow is measured between these two ports during both inspiration and expiration. From the measured flow (flow rate, peak flow) and pressure (end-expiratory, plateau, maximum and minimum) values, the tidal and minute volumes are computed during both inspiration and expiration. Dynamic compliance of the respiratory system is determined continuously using the end-inspiratory plateau pressure. The flow sensor has a deadspace of 9.5 ml, and its resistance is 0.5 cm H_2O/30 litre min^{-1}. Two loops are drawn from the measured variables—the flow–volume (FV) and the pressure–volume (PV) loop, which are displayed continuously (fig. 2), stored and updated at each breath. Changes in compliance and airway resistance or the expiratory flow characteristics of the whole respiratory system (lungs and thorax, tracheal tube) are illustrated continuously and visually by the changing form of each loop and may be compared with the baseline curves [2, 3]. Compromised airway patency or incorrect placement of the tracheal tube may alter the PV and FV curves in a particular way, which may help to detect the origin of the problem and its effect on ventilatory mechanics.

We report six patients in whom continuous spirometry helped to recognize or to confirm inadequacy of ventilation.

CASE REPORTS

Inadvertently misplaced tracheal tubes

Patient No. 1: endobronchial intubation. A young woman was undergoing a small procedure on the neck. Her trachea was intubated without difficulty. Breath sounds were equal bilaterally by auscultation, peak inspiratory airway pressure and compliance were normal. After the patient's head was turned for surgery, the high pressure alarm sounded and a decrease in compliance accompanied the right shift of the displayed PV curve (fig. 3). Arterial oxygen saturation and end-tidal carbon dioxide concentration were unchanged. On auscultation, no breath sounds were detected on the left side of the chest and endobronchial displacement of the tracheal tube was suspected.

Withdrawing the tracheal tube by 3 cm resulted in normal PV and FV loops and bilaterally equal breath sounds.

Patient No. 2: oesophageal intubation. An 83-yr-old woman was undergoing right lobectomy. General anaesthesia was induced and an oral double-lumen endobronchial tube inserted without visualization of the vocal cords. The common connector of the tube was attached to the flow sensor of the Ultima SV and the ventilator. During routine auscultation of the

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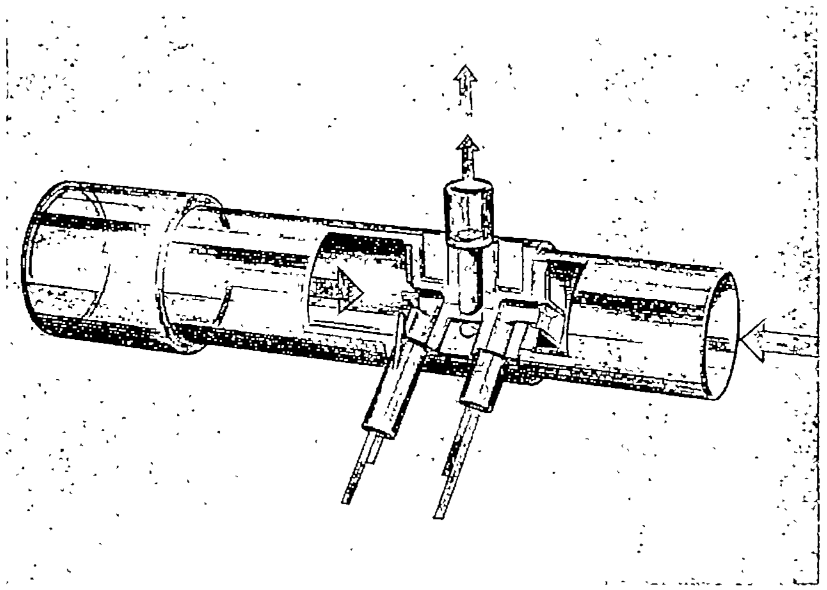

FIG. 1. Section of the D-lite flow sensor, with the two fixed resistances and a gas sampling port.

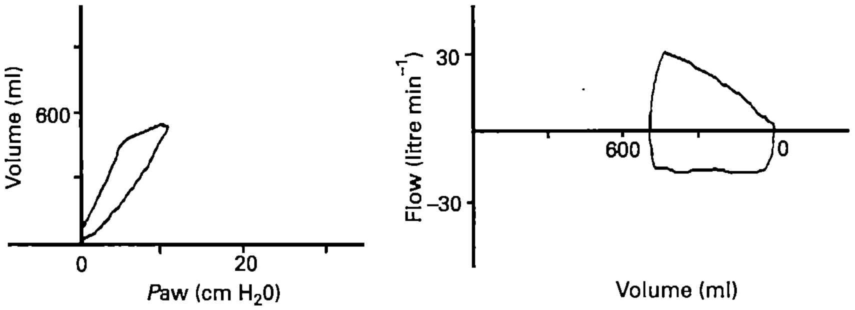

FIG. 2. Normal pressure–volume (left panel) and flow–volume (right panel) curves recorded in a paralysed patient with the trachea intubated undergoing mechanical ventilation.

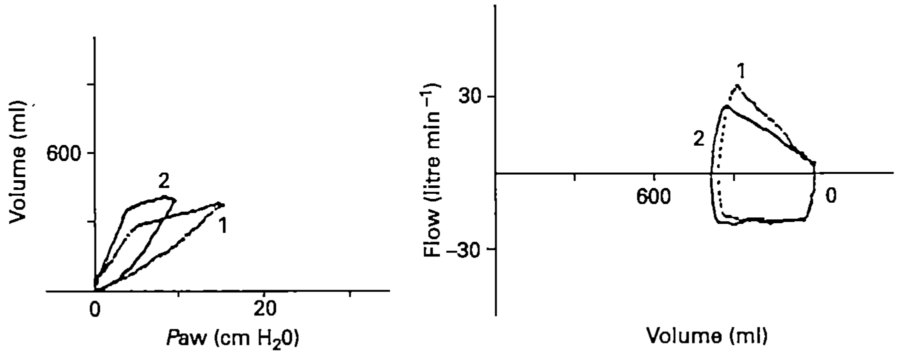

FIG. 3. Patient No. 1: endobronchial intubation. Pressure–volume (left panel) and flow–volume (right panel) curves when the tracheal tube was displaced into the right mainstem bronchus (1) and when withdrawn 3 cm into the trachea (2). Note the right- and downward shift of the pressure–volume curve and the decreased expiratory flow seen on the flow–volume curve when the tube was positioned endobronchially.

chest, distant breath sounds were reported and a non-compliant PV loop and distortion of both the inspiratory and expiratory part of the FV loop were displayed (fig. 4), accompanied by small expiratory and inspiratory tidal volumes. The concomitant lack of detectable carbon dioxide suggested oesophageal intubation. A second laryngoscopy confirmed oesophageal placement of the double-lumen tube; it was removed and its position corrected.

Increased inspiratory pressure from mechanical causes

Patient No. 3 : kinking of the tracheal tube. A 30-yr-old woman underwent general anaesthesia for gynaecological laparoscopy. Shortly after the position of the laparoscope was changed by the surgeon, increased inspiratory airway pressure and decreased compliance were noted, with a right shift of the PV loop. On the FV loop, inspiratory and expiratory

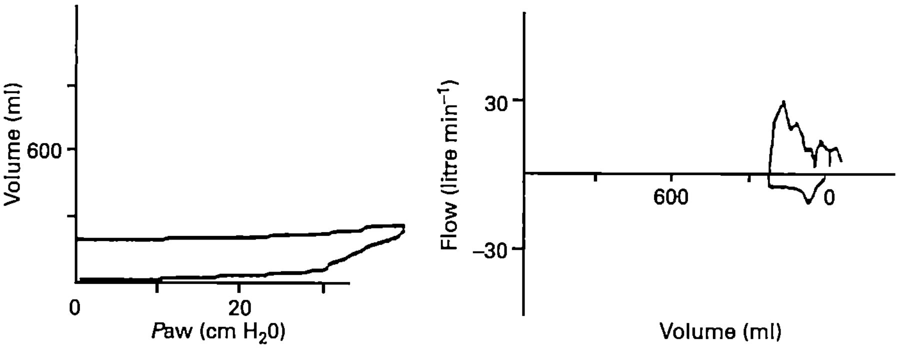

FIG. 4. Patient No. 2: oesophageal intubation. The area of the pressure–volume loop (left panel) is enlarged; increased inflation pressure was necessary to deliver a small volume into the non-compliant oesophagus. The flow–volume loop (right panel) has irregular inspiratory and expiratory parts.

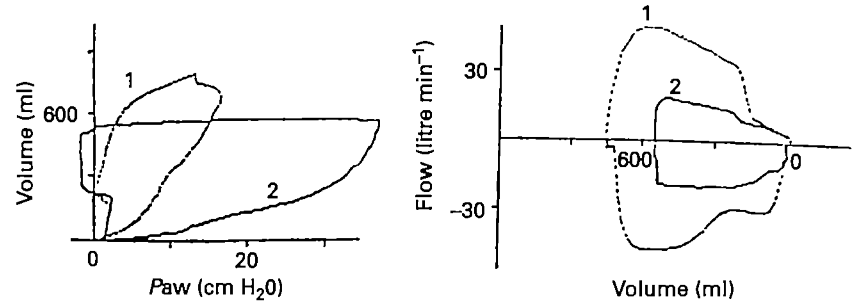

FIG. 5. Patient No. 3: tracheal tube kinking. Pressure–volume (left panel) and flow–volume (right panel) loop recorded after induction of anaesthesia (1) and when the tracheal tube was partially kinked (2) during laparoscopy. Note the right shift and enlarged area of the PV curve with increased inspiratory pressure, and the diminished inspiratory and expiratory flow of the FV curve.

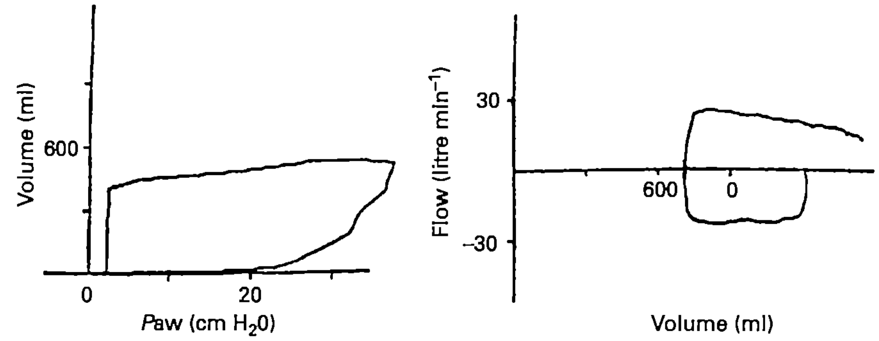

FIG. 6. Patient No. 4: compression of the right hemithorax caused by abdominal retractors. The PV curve (left panel) is shifted to the right, its area enlarged, with increased inspiratory pressure. End-expiratory pressure was 14 cm H_2O. On the FV curve (right panel), note that exhalation is not yet complete at the beginning of the new inspiratory phase.

flows were diminished and both limbs became horizontal, with decreased inspiratory and expiratory tidal volumes (fig. 5). Lifting the drapes from the patient's head revealed partial kinking of the tracheal tube, caused by the gynaecologist's elbow.

Patient No. 4: chest compression. A 14-yr-old boy was undergoing exploratory laparotomy under general anaesthesia for removal of an extensive retroperitoneal tumor. During exploration, increased inspiratory and end-expiratory pressures were accompanied with audible wheezes and abnormal configuration of the expiratory parts of the PV and FV loops. The expiratory part of the FV curve did not return to the zero volume axis (fig. 6). On questioning, the surgeon disclosed that the subcostally placed abdominal retractor almost completely compressed the right lung. Repositioning the retractor terminated the wheezing and resulted in normal ventilatory data.

Patient No. 5: double-lumen tube dislodgement. A 67-yr-old man's trachea was intubated with a left-sided double-lumen endobronchial tube for a right pneumonectomy. The surgical dissection was extremely difficult because of extensive adhesions. One-lung ventilation was well tolerated. However, the surgeon was asked on several occasions to refrain from excessive stretching of the hilum. Suddenly, a completely distorted FV curve (fig. 7) was seen, with inspiratory airway pressure greater than 60 cm H_2O and inability to ventilate the lung. Dislodgement of the double-lumen tube was diagnosed and confirmed by fibreoptic bronchoscopy.

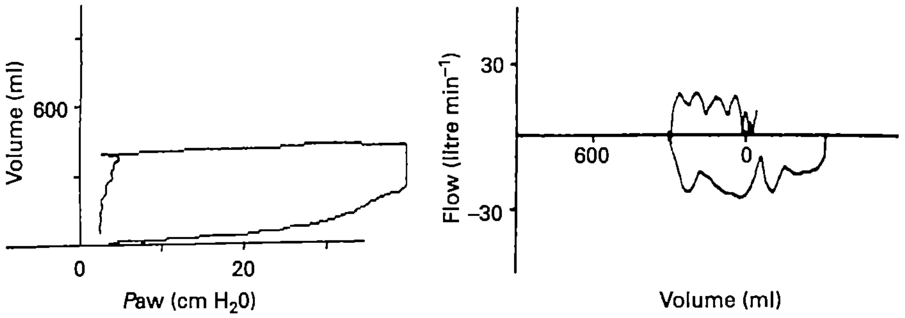

FIG. 7. Patient No. 5: dislodged double-lumen endobronchial tube. FV curve recorded when the double-lumen endobronchial tube was dislodged from the left mainstem bronchus, and twisted to the other side. Note the highly irregular inspiratory and expiratory limb of the FV loop, the right- and downward shifted PV loop with enlarged area.

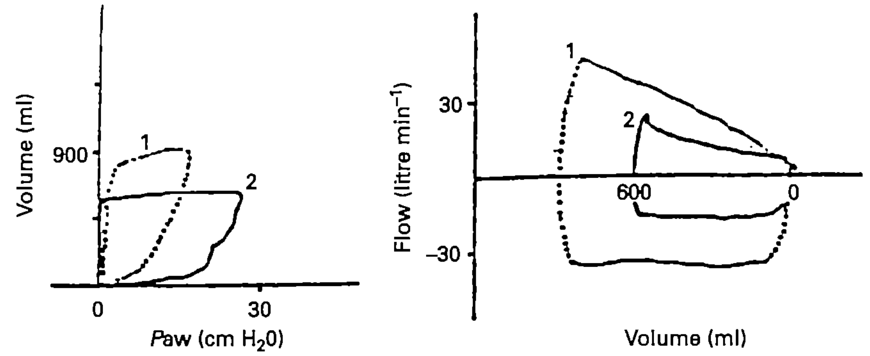

FIG. 8. Patient No. 6: increased inspiratory pressures caused by decreased airway calibre. PV (left panel) and FV (right panel) loops recorded during an episode of bronchospasm (2). Increased inflation pressure, decreased compliance and right shift of the PV loop (2) may be observed, in comparison with the loop recorded previously (1). The bowing configuration of the expiratory part of the FV loop (2) is characteristic for small airways obstruction.

Increased inspiratory pressure caused by decreased airway calibre

Patient No. 6: bronchospasm. A 45-yr-old asthmatic male was undergoing heart transplantation. Before termination of cardiopulmonary bypass, pulmonary ventilation was re-established. Hyperinflated lungs were protruded through the sternotomy and auscultation revealed bilateral wheezing. On the screen of the ventilatory monitor, a right- and downward-shifted PV curve was noted, with a scooped-out expiratory limb of the FV loop (fig. 8). Increased inspiratory airway pressure, decreased compliance and decreased tidal volume accompanied the reduction in expiratory flow. Because the patient gave a history of reactive airway disease, bronchospasm was considered and i.v. bronchodilator therapy was started. Within a few minutes, bronchospasm subsided gradually and cardiopulmonary bypass was discontinued successfully.

DISCUSSION

Monitoring lung mechanics (pressure–volume and flow–volume loops) has been used traditionally in the laboratory and intensive care unit [4, 5]. As a result of advances in computer technology, these measurements have now been introduced into anaesthetic practice [1–3, 6].

The displayed passive FV loop (fig. 2, right) has two components: the lower, smoothly curved inspiratory part and the upper, triangular expiratory part, where the apex represents peak expiratory flow [7]. In patients with the trachea intubated, undergoing mechanical ventilation, the shape of the inspiratory limb is influenced mainly by the ventilator and does not provide valuable information about the patient's ventilatory system. As exhalation is passive, the expiratory part of the FV loop is determined by the mechanical properties of the ventilatory system (including the resistance of the tracheal tube).

The slightly oval PV loop (fig. 2, left) has an ascending lower limb, which represents the increasing inspiratory pressure necessary to inflate the lung and a descending upper curve, which reflects the decreasing pressure during deflation of the lung [8]. The slope of the curve is the dynamic compliance and the area of the curve is mainly a function of airway resistance [9].

In patients with the trachea intubated during anaesthesia, resistance of the total ventilatory system is influenced mainly by the characteristics of the tracheal tube [8]. After correct initial placement, displacement of the tube may occur, its lumen may be obstructed by secretions or kinking and it may be dislodged completely, resulting in an increase in peak airway pressure [8].

Decreasing airway calibre resulting from bronchoconstriction is associated with increased airway resistance and increased inspiratory pressure. Auscultation and inspection of the motion of the chest wall can provide important diagnostic clues. However, breath sounds may be difficult to interpret in some pathological conditions or the chest may be inaccessible for auscultation. Without additional information, it cannot be ascertained if the site of increased resistance is in the tracheal tube or the lung. As changes in airflow resistance and compliance are illustrated visually by the changing configuration of PV and FV loops, these may be used to differentiate the origin of increased inspiratory pressure.

Enlarged areas of the PV curve (increased resistance) with right- and downward shift of the slope (decrease in compliance) are seen in most of the conditions associated with increased peak airway pressures. Inspecting the expiratory limb of the corresponding FV curve may offer more detailed information: kinking of the tracheal tube alters both the inspiratory and expiratory limb to about the same degree and a uniform manner (fig. 5), external obstruction distorts the expiratory limb more (fig. 6) and impingement of the tip against the airway wall or a tidal volume delivered into the non-compliant oesophagus both result in a grossly distorted FV loop (fig. 4).

Bronchoconstriction also is associated with increased airway resistance [4]. The area of the pressure–volume loop is enlarged (fig. 8), with right shift of the slope; greater inspiratory pressure is necessary to deliver a given volume. The flow–volume loop reveals uneven lung emptying with the scooped-out, convex configuration of the expiratory limb. Bronchoconstriction is a dynamic phenomenon, and its time course may be followed easily by the increasing or decreasing convexity of the expiratory limb as successive FV curves are compared. There is evidence in the literature that the severity of airway obstruction and response to bronchodilators may be estimated by assessment of ventilatory mechanics [10]. These cases imply that continuous monitoring of pressure–volume and flow–volume loops may be useful in detecting and diagnosing airway problems.

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COMMENTARY

POSTOPERATIVE ANALGESIA IN CHILDREN USING CONTINUOUS S.C. MORPHINE

R. McNICOL

SUMMARY

Sixty children (7 months–20 yr; mean 6.5 yr, median 7–8 yr, mode 1–2 yr) undergoing major surgery received a balanced technique of general anaesthesia combined with bupivacaine as a single injection extradural or peripheral nerve block. Postoperative analgesia consisted of a subcutaneous infusion of morphine 1 mg kg^{-1} body weight in 20 ml of sodium chloride 1 mol litre^{-1} at a rate of 0.3–0.5 ml h^{-1}, controlled by the nursing staff in the surgical ward. Monitoring included Sp_{O_2}, *pain, sedation and nausea/vomiting scores. Infusions were used for a mean of 38.8 h (range 17–80 h). Ninety-seven percent of recordings of* Sp_{O_2} *were greater than 94% and only one recording in 2361 was less than 90%. Ninety-four percent of pain scores indicated either no pain or slight pain; 1% indicated severe pain. On the order of the medical staff, seven children had the rate of infusion of morphine increased to 0.6 ml kg^{-1} h^{-1} because of high pain scores. Sedation scores compatible with children being either awake or asleep but rousable by speech alone were recorded on 99.7% of occasions. No child at any time was unrousable. Of 1248 nausea/vomiting scores, only 2.8% indicated the presence of these side effects; in only two children were they thought to be troublesome. As a result of this audit, nursing staff have been permitted to increase the rate of infusion of morphine to 0.6 ml kg^{-1} h^{-1} if required.* (Br. J. Anaesth. 1993; **71**: 752–756)

KEY WORDS

Anaesthesia: paediatric. Analgesia: postoperative. Measurement techniques: pulse oximetry.

Subcutaneous morphine has been used in adult practice as a continuous infusion for the relief of postoperative pain [1, 2]. It has been advocated for use in children as an intermittent "on demand" technique via an indwelling subcutaneous cannula [3]. Lloyd-Thomas [4] has suggested that, if used as a continuous s.c. infusion, the required dose of morphine should not differ much from the i.v. regimen described by Bray [5]—20 μg kg^{-1} h^{-1}; such a regimen has become common practice in our hospital. The aim of this study was to appraise this technique critically, using a postoperative monitoring procedure which has developed with this and other methods of preventing postoperative pain.

PATIENTS AND METHODS

Thirty male and 30 female children undergoing major abdominal, urological or orthopaedic surgery (table I) were anaesthetized using a balanced technique of general anaesthesia in which intraoperative analgesia was established after induction of anaesthesia with a regional block using bupivacaine

TABLE I. *Surgical procedures undertaken in the study*

Surgical procedures	No. patients
General surgery	
Laparotomy	11
Fundoplication	1
Urological surgery	
Bilateral pyloplasty	2
Unilateral pyloplasty	6
Re-implantation of ureters	4
Repair of urogenital sinus	1
Insertion of artificial sphincter	2
Bladder augmentation	1
Closure of ureterostomy	1
Orthopaedic procedures	
Femoral derotation osteotomy	5
Unilateral soft tissue correction of club foot	4
Open reduction of congenital dislocation of the hip	3
Femoral rodding for osteogenesis imperfecta	2
Robert Jones procedure	2
Klisic's procedure	2
Ilizarov procedure	3
Adductor division	2
Subtalar fusions	2
Bone grafts of tibia	2
Leg lengthening	1
Other osteotomy of femur	1
Psoas + ham strings + adductor division	1
Bilateral soft tissue correction of club feet	1

TABLE II. *Regional blocks used*

Block	No. patients
Extradural	
Caudal	34
Lumbar	17
Thoracic	3
Peripheral nerve	
Fascia iliaca	4
Sciatic/saphenous	1
Abdominal field	1

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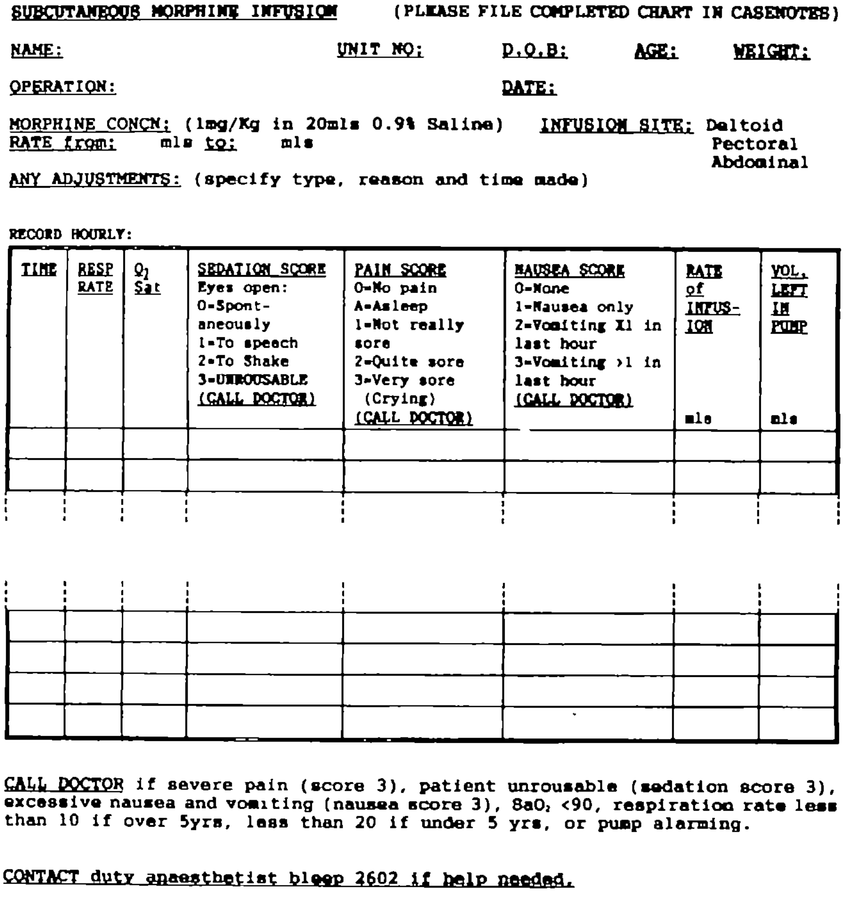

SUBCUTANEOUS MORPHINE INFUSION (PLEASE FILE COMPLETED CHART IN CASENOTES)

NAME: **UNIT NO:** **D.O.B:** **AGE:** **WEIGHT:**

OPERATION: **DATE:**

MORPHINE CONCN: (1mg/Kg in 20mls 0.9% Saline) **INFUSION SITE:** Deltoid
RATE from: mls **to:** mls Pectoral
Abdominal

ANY ADJUSTMENTS: (specify type, reason and time made)

RECORD HOURLY:

TIME	RESP RATE	O_2 Sat	SEDATION SCORE Eyes open: 0=Spont-aneously 1=To speech 2=To Shake 3=UNROUSABLE (CALL DOCTOR)	PAIN SCORE 0=No pain A=Asleep 1=Not really sore 2=Quite sore 3=Very sore (Crying) (CALL DOCTOR)	NAUSEA SCORE 0=None 1=Nausea only 2=Vomiting X1 in last hour 3=Vomiting >1 in last hour (CALL DOCTOR)	RATE of INFUS-ION mls	VOL. LEFT IN PUMP mls

CALL DOCTOR if severe pain (score 3), patient unrousable (sedation score 3), excessive nausea and vomiting (nausea score 3), SaO_2 <90, respiration rate less than 10 if over 5yrs, less than 20 if under 5 yrs, or pump alarming.

CONTACT duty anaesthetist bleep 2602 if help needed.

or Dr. Home no:

FIG. 1. Final format of monitoring chart.

(table II). The ages of the children were from 7 months to 20 yr (mean 6.5 yr, median 7–8 yr, mode 1–2 yr); five infants aged 7 months to 1 yr were included. Weights were 6.6–60 kg (mean 23.1 kg).

At the commencement of surgery, a 24-gauge Neoflon cannula was inserted s.c. over the deltoid muscle. It was connected to a 60-ml syringe containing morphine sulphate 1 mg/kg body weight, made up to 20 ml with normal saline (20 μg/kg body weight contained in 0.4 ml). The syringe was connected to a syringe pump by spiral extending monitoring tubing and the initial infusion rate was 0.4 ml h^{-1}.

Monitoring was carried out in a high dependency area of the normal surgical ward (near the nursing station) and consisted of hourly readings made by the regular surgical ward nursing staff (fig. 1). This aimed to assess the patient's response to morphine (Sp_{O_2}, ventilatory frequency, sedation, pain and nausea) and the efficiency of the syringe pump (rate of infusion and volume left in syringe). Oxygen saturation was measured using an Ohmeda Biox 3700 oximeter which was set to alarm if Sp_{O_2} decreased to less than 90%. All patients breathed room air. The rate of infusion was prescribed to run at 0.3–0.5 ml h^{-1} and the nursing staff were instructed that they may vary this as necessary and reduce or stop it if the situation so warranted; however, permission to increase the infusion to rates greater than 0.5 ml h^{-1} had to be sought from medical staff. The nursing staff had clear instructions to call named medical staff if any of the criteria named on the postoperative chart were seen to develop.

RESULTS

The results are summarized in table III. The majority of pain scores (94%) were 0 or 1, indicating no pain or mild pain. Eleven patients had a pain

TABLE III. *Analysis of recordings from postoperative pain charts*

Number of patients: 60
Total number of recordings: 2361
Duration of infusion (Hrs) 17–80 (38.8)—Range (mean)

Pain scores
- 0–1 $n = 2220$ (94%)
- 2 $n = 120$ (5%)
- 3 $n = 21$ (1%)
- Mean pain score of all recordings = 0.47

Sedation scores
- 0–1 $n = 2353$ (99.7%)
- 2 $n = 8$ (0.3%)
- 3 $n = 0$ (0%)
- Mean sedation score of all recordings = 0.45

Sp_{O_2} (%)
- Minimum for each patient: mean 93% (range 86–98%)
- $Sp_{O_2} < 94\%$ $n = 75$ (3%)
- $Sp_{O_2} < 93\%$ $n = 30$ (1%)
- $Sp_{O_2} < 90\%$ $n = 1$ (0.04%)

Nausea scores ($n = 1248$)
- 0 $n = 1213$ (97.2%)
- 1 $n = 18$ (1.4%)
- 2 $n = 16$ (1.3%)
- 3 $n = 1$ (0.1%)

TABLE IV. *Morphine consumption in postoperative period (number of patients or mean (SEM))*

	Postoperative period (h)													
	6	12	18	24	30	36	42	48	54	60	66	72	78	84
No. patients	60	60	60	55	46	43	42	19	13	8	6	2	2	2
Rate of infusion	0.38	0.38	0.32	0.32	0.27	0.28	0.27	0.22	0.24	0.25	0.175	0.23	0.38	0.15
(ml h^{-1})	(0.1)	(0.1)	(0.13)	(0.13)	(0.14)	(0.1)	(0.1)	(0.15)	(0.11)	(0.07)	(0.03)	(0.03)		
Mean rate of infusion														
(ml h^{-1})	←---0.35---→				←---0.266---→				←---0.22---→					
(μg kg^{-1} h^{-1})	←---17.5---→				←---13.3---→				←---11.0---→					

score of 3 (severe pain) at some time in the postoperative period; in six of them it occurred only on one occasion. One child was noted to be in severe pain on five occasions in the 48 h after bilateral pyloplasty and received 1-ml "top-ups" on the orders of the resident medical staff. As a direct result of having a high pain score noted, seven other children had the rate of infusion of morphine increased to 0.6 ml h^{-1} or more at some time in the postoperative period, on the orders of the medical staff.

Virtually all the children had sedation scores indicating that they were awake or could be roused by speaking to them. No child was unrousable at any time (score 3).

Ninety-seven percent of Sp_{O_2} recordings were greater than 94%; only one recording less than 90% was noted. This was in a 12-yr-old girl who underwent lengthening of a tibia on one leg and of a femur on the other. Sp_{O_2} recordings taken 1 h before and 1 h after the abnormal result were normal and the decreased value was not associated with undue sedation.

Not all patients had nausea/vomiting scores recorded on their postoperative charts, but as the charts evolved it became obvious that this would be helpful. For 26 of the patients there was a column on the chart for non-specific comments only; one patient was noted to require an antiemetic. The charts of eight patients had a column asking specifically for "comments, eg nausea or vomiting"; none of these recorded any relevant comments. The remaining 26 patients had the final format of chart including a nausea/vomiting score, for which there were 1248 recordings. Thirteen of these patients complained of various degrees of nausea or vomiting: nine vomited once in 1 h (five of them vomited on only one occasion in the postoperative period); of the other four, two vomited twice in the first 48 h after operation—one on three occasions and the other on four occasions.

The rate of infusion of morphine did not vary greatly during the first 24 h and reduced gradually over the remainder of the postoperative period (table IV).

No complications were observed at the cannula sites in any child at the completion of the infusion. On two occasions, the cannula was removed accidentally, either by the child or by the nursing staff: one was replaced immediately with no increase in pain; the other was discarded by nursing staff, but had to be replaced later when the child began to complain of pain.

DISCUSSION

Postoperative pain relief for children following major surgery is less than perfect. Mather and Mackie drew attention to the reluctance of anaesthetists to prescribe opioid analgesia and of nursing staff to administer such medication, even if prescribed, with the result that only 25% of children in their study had adequate pain relief on the day of surgery [6]. The reasons for this are understandable, the main one being a fear of overdosage. A second and no less important one is the reluctance of paediatric nurses to use the i.m. route for drug administration; this was highlighted in a recent tragic case in which an infant received an inappropriate dose of morphine by the rectal route [7]. In order to avoid repeated i.m. injections, Lavies and Wandless [3] used indwelling cannulae for intermittent injections of morphine in children undergoing major abdominal surgery, but even this caused some discomfort in 40% of children in the study.

Continuous s.c. infusions of morphine would appear to be superior to intermittent injections, in that a smaller volume of morphine is injected over a short period of time and breakthrough pain, the main drawback of "on demand" analgesia, is avoided. Lloyd-Thomas [4] has suggested that a dose of 20 μg kg^{-1} h^{-1} should be sufficient to prevent pain caused by major surgery. This is similar to the i.v. dose of morphine used by Bray [5]. There is good reason for Lloyd-Thomas to believe that the s.c. route should provide pain relief comparable to that obtained with the i.v. route, as Waldmann and colleagues [1] showed, in a study in adults, that not only did both these routes provide similar postoperative analgesia, but also the serum concentrations of morphine produced did not differ significantly.

The s.c. route of administration would appear to have several advantages over the i.v. route in paediatric practice. The success of the i.v. route is dependent on the patency of small veins and small cannulae, and in children's hospitals it is by no means uncommon for i.v. infusions to become blocked or for cannulae to become kinked because of the movement or positioning of joints. In theory, the s.c. route should be safer also because delivery of morphine is slower; in the event of equipment failure or overdosage for other reasons, any effect upon the child would be less rapid. When use of continuous opioid infusions, either s.c. or by PCA, began in our hospital, a decision was made that they could be carried out only in a high dependency area—not necessarily in a high dependency or intensive care unit, but in a normal postoperative surgical ward in the presence of an adequate number of trained nursing staff and only when pulse oximetry was available for each individual child. However, analysis of the pain charts in this study has revealed a very low incidence of desaturation and it may be acceptable to monitor these patients without oximetry, provided attention is paid to the other recordings listed in the postoperative pain chart. *It is important to note that, in our patients s.c. morphine is administered as part of one particular anaesthetic technique—namely, following an intraoperative single-shot regional block using bupivacaine.* All patients in this audit were devoid of pain on recovery from anaesthesia. All blocks were assessed carefully in the postanaesthetic recovery area and had to be effective before patients were returned to the wards. As the blocks gradually regressed, the morphine infusion became the principal method of pain relief. From previous experience, we know that it is important to achieve good analgesia immediately after operation if a continuous technique is to be used during the next day or two. If a block is considered to have failed, any pain should be relieved by bolus i.v. administration of opioids before the infusion is commenced.

The safety of this technique is demonstrated by the sedation scores and oxygen saturations. No child was unrousable at any time and nearly all Sp_{O_2} values were greater than 94%; only one recording was less than 90%. These two parameters are the most valuable in assessing the response of patients to opioid administration. In adults, ventilatory frequencies have been shown to be of little value [8, 9] and are even less so in children, in whom many factors may combine to alter them—age of the child, pain, hunger, sleep, fear or emotion [10]. There is little relationship between ventilatory frequency and oxygen saturation, and for this reason all patients had Sp_{O_2} recorded hourly. When room air is breathed, any significant respiratory depression associated with an increase in alveolar carbon dioxide partial pressure is reflected in a decrease in PA_{O_2} and Sp_{O_2}. Thus, despite the small incidence of desaturation in this audit, it has become common practice in our hospital to monitor Sp_{O_2} regularly in all children receiving continuous infusions of morphine by either s.c. infusion or PCA [11].

Although some nausea and vomiting was noted, this accounted for only 2.8% of 1248 recordings. The lack of spontaneous comments about this side effect reflected the poor design of our initial postoperative charts. In the final chart, a direct question was asked. Nausea and vomiting after paediatric surgery is very common and in a large audit (20000+) of a variety of procedures, most of which were of a minor nature, Cohen, Cameron and Duncan [12] found this was a significant problem in more than 30% of children studied, most often, but not always, in association with the administration of opioids. The incidence of nausea and vomiting in the present study was similar despite the number of major surgical and intra-abdominal procedures performed.

The postoperative charts proved to be popular with the nursing staff. Initially, they were used to ensure that the technique was safe. However, they soon developed into an essential part of postoperative management and now form the basis of a paediatric acute pain service.

It is interesting to note that the morphine consumption recorded in the first 24 h (17.5 μg kg^{-1} h^{-1}) was less than that recorded by Irwin, Gillespie and Morton [13], whose patients used morphine 20.3 μg kg^{-1} h^{-1} delivered by a disposable PCA system, and by Lawrie and colleagues [14], whose patients consumed 21.0 μg kg^{-1} h^{-1} via a Graseby PCA system.

There is no doubt that PCA has a role in paediatric practice, but its main disadvantage is the requirement that children be old enough and intelligent enough to use it. These problems may be overcome by using s.c. infusions of morphine and, indeed, many children in our study were infants, some of whom, although not unduly young, suffered from cerebral palsy with associated lack of motor power, intellect, or both.

In conclusion, a balanced technique of general anaesthesia using bupivacaine during operation, followed by an s.c. infusion of morphine, may provide dependable analgesia for many hours after operation. Enthusiastic nursing staff keen to take advantage of a postoperative monitoring regimen are essential for the smooth performance of what is, in essence, an acute pain service. Analysis of the postoperative pain charts in this audit has revealed a low incidence of oxygen desaturation, which highlights the safety of the technique and suggests that it may be possible to use it when pulse oximetry is not available. However, regular use of pulse oximetry has definite advantages and should be used if available. Our original upper limit of infusion (0.5 ml h^{-1}) may be increased safely to 0.6 ml h^{-1}, and nursing staff are now permitted to use this infusion rate if required.

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British Journal of Anaesthesia 1993; 71: 757P–771P

ABSTRACTS

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

OXFORD MEETING

JULY 9–10, 1993

(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

ASSESSMENT OF COUGH PEAK FLOW RATE AND PEAK VELOCITY TIME BY TUSSOMETRY IN MALES AND FEMALES

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The differences in phonation between males and females are thought to occur as a result of the anatomical differences in the larynx [1]. However, it is not known if there are any differences in cough dynamics between the sexes. We have used tussometry to investigate this.

Tussometry is a non-invasive method of assessing vocal cord function. The tussometer comprises an anaesthetic face mask attached to a pneumotachograph system. The pressure differential across this is used to derive airflow using a Gaeltec flowmeter; the resultant waveform is displayed on a BBC microcomputer as a flow time wave, allowing measurement of the cough peak flow rate (CPFR) and the time taken to achieve this, the peak velocity time (PVT). The PVT is determined by laryngeal opening at the onset of a cough and correlates with vocal cord function [2].

After familiarization with the equipment, 100 healthy, non-smoking adults (50 male) were asked to perform a voluntary cough manoeuvre into the tussometer whilst seated. Each volunteer coughed at four different lung volumes, ranging from total lung capacity to functional residual capacity. All cough manoeuvres were performed with maximum effort.

There was a strong positive correlation between PVT and CPFR (fig. 1) in both males ($P < 0.001$) and females ($P < 0.001$). However, there was a statistically significant difference in the regression lines between the two groups ($P < 0.001$). This may be related to anatomical differences in laryngeal structure and may have implications when using tussometry to assess laryngeal function.

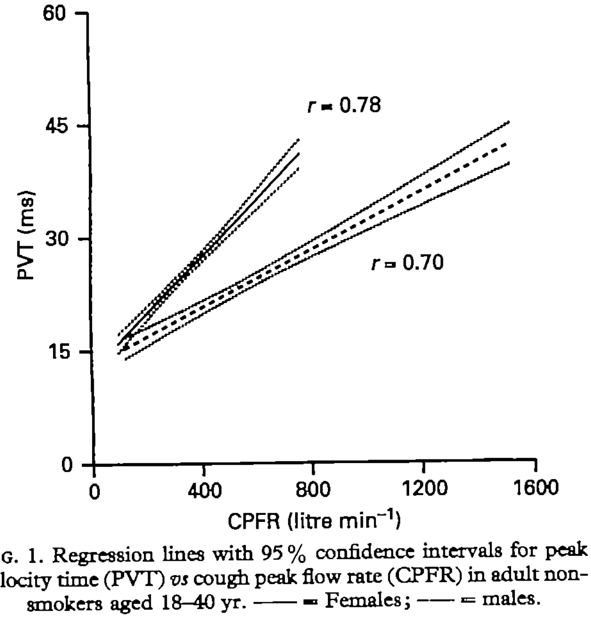

FIG. 1. Regression lines with 95% confidence intervals for peak velocity time (PVT) *vs* cough peak flow rate (CPFR) in adult non-smokers aged 18–40 yr. —— = Females; —— = males.

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A PILOT STUDY OF THE EFFECT OF HALOTHANE ON HUMAN CILIARY BEAT FREQUENCY *IN VITRO*

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Impairment of mucociliary transport rate (MTR) after general anaesthesia may predispose patients to postoperative atelectasis [1]. MTR is dependent on the visco-elastic properties of the mucus and co-ordinated ciliary function [2].

The method we used comprised a television video modification of the transmitted light technique, utilizing a photo-diode, video and phase contrast microscopy [3]. A power spectrum of cilia beat frequency (CBF) was determined using the Anadat data analysis program.

Twenty-four non-smoking volunteers, aged 22–35 yr, with no history of atopy, URTI or recent medications were recruited. A single nasal brushing was obtained without local anaesthesia from each volunteer using a standard bronchial biopsy brush. Eighteen volunteers, divided into three groups of six, were recruited for the study of halothane exposure at 0.9%, 1.8% and 5.7%. Cilia samples were divided into two test tubes containing MDE 199

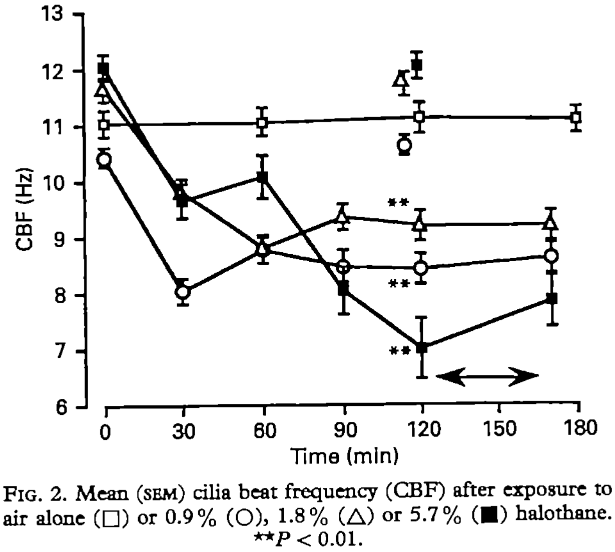

FIG. 2. Mean (SEM) cilia beat frequency (CBF) after exposure to air alone (□) or 0.9% (○), 1.8% (△) or 5.7% (■) halothane. $^{**}P < 0.01$.

culture media. One test tube was exposed to halothane in air and the other was exposed to air alone. CBF of the samples exposed to halothane was measured at 0, 30, 60, 90 and 120 min, and after an air washout period lasting 50 min. CBF of the samples exposed to air alone was measured at 0 and 120 min. Six further volunteers providing control samples were exposed to air alone. CBF of the control samples was measured at 0, 60, 120 and 180 min.

CBF measurements were made from four undisrupted ciliated edges of epithelial sheets of at least 60 μm in length. Four separate measurements were made from each edge. Therefore, for each time point a total of 16 readings was made. Samples were kept at 37 °C.

There was an increase in variability of CBF after exposure to halothane at all concentrations (fig. 2). There was a significant reduction in CBF compared to controls after 120 min of exposure to halothane at all concentrations.

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ACCURATE RECORD OF VIEW AT LARYNGOSCOPY

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View at laryngoscopy remains the generally accepted criterion for recording difficulty with tracheal intubation. A photographic method has been described which allows measurement of laryngeal diameter [1]. Early experience with this technique indicated that although sharp focusing on the larynx was relatively easy, the view recorded was not necessarily consistent with what the anaesthetist perceived it to have been. The reason became obvious when video recording was used instead of still photography. The clinician builds up a view by panning and the image perceived depends more on this than single "snapshots". Because this is not generally taken into account and laryngoscopy assessed in a systematic way, it is easy to understand why differences in observation technique will alter the "view" in the same subject under similar circumstances.

We determined if the photographic method could be applied to video imaging for accurate recording of view at intubation. Simple bench tests were used to simulate intubation by observing paired cards of appropriate height. These were to represent vocal cords of different sizes. In addition, the cards were moved forwards and backwards relative to one another to demonstrate the relevance or otherwise of accurate focusing. The photographer focused on the left of the "vocal cords" each time and photographic and video imaging of varied cord size and separation were compared with actual card sizes. The photographs were taken with a Nikon FM 2 camera with a Nikon micro lens and a magnification ratio of 1:4. As for the photographic method described, the images were compared with standard grids at the same focal distance as the initial view. The video images were recorded with a Panasonic M10 VHS Camcorder with a macro lens. For the video views, the focus was set to manual and kept fixed. The camcorder position was adjusted until the image was in focus. Similar arrangements were made for the recording of a measuring grid.

Provided the image is sharply focused, accuracy to within 1 mm is easily possible with still photography. The poorer colour resolution and less sharp focusing make the video measurement much less accurate. For clinical trials where an accurate record of the view at laryngoscopy may be required, a combination of both may be appropriate.

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OXYGEN UPTAKE DURING REBREATHING IN A MAPLESON A SYSTEM

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Some evidence suggests that oxygen uptake ($\dot{V}O_2$) is increased by rebreathing from the Mapleson A system [1, 2]. An increase of 30–87% in $\dot{V}O_2$ has been reported [2] under rebreathing conditions defined by Kain and Nunn [1] and Humphrey [3]. We used a standard method of measurement of oxygen uptake to assess this possibility.

We studied 14 ASA I volunteers (eight male), who gave informed verbal consent to the study. Resting minute ventilation ($\dot{V}_E$), oxygen consumption and production of carbon dioxide were measured in each subject using a Douglas bag. The subjects then breathed via a mouthpiece from the Mapleson A system for 8 min, after which expired gas was collected from the spill valve of the system, over duplicate 2-min periods, into Douglas bags and analysed for concentrations of oxygen and carbon dioxide by mass spectrometry and for volume using a Tissot spirometer. The fresh gas flow into the system was determined as a ratio of the resting $\dot{V}_E$: 14 subjects were studied at $\dot{V}_F/\dot{V}_E$ ratios of 1.3, 0.8, 0.6 and 0.4 and a further three subjects at ratios of 1.3, 0.8 and 0.6 only. The order of the fresh gas flows was randomized and blind to the subject. The degree of rebreathing was assessed by measuring inspired concentration of carbon dioxide at the lips by mass spectroscopy.

Rebreathing occurred in 13 of 14 subjects with a $\dot{V}_F/\dot{V}_E$ ratio of 0.6 and occurred markedly in all subjects measured at a $\dot{V}_F/\dot{V}_E$ ratio of 0.4 (table I).

There was no significant difference (ANOVA) between any of the measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ (not illustrated).

TABLE I. *Mean* (SD) *oxygen uptake* ($\dot{V}O_2$) *at different* $\dot{V}_F/\dot{V}_E$ *ratios*

$\dot{V}_F/\dot{V}_E$ (Desired)	$\dot{V}_F/\dot{V}_E$ (Actual)	$\dot{V}O_2$ (ml min^{-1} kg^{-1}) (STPD)
1.0 (Rest)	1.0	3.38 (0.51)
0.4	0.49 (0.06)	3.35 (0.40)
0.6	0.66 (0.04)	3.25 (0.47)
0.8	0.87 (0.03)	3.18 (0.39)
1.3	1.43 (0.19)	3.19 (0.41)

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EFFECT OF TWO SUBANAESTHETIC CONCENTRATIONS OF HALOTHANE ON THE PERIPHERAL AND CENTRAL CHEMOREFLEX LOOP IN MAN

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It is believed generally that 0.1 MAC of halothane depresses the ventilatory response to hypoxia because of its effect on peripheral chemoreceptors. The effect of subanaesthetic concentrations of halothane on the ventilatory carbon dioxide response of peripheral chemoreceptors has not been investigated in man.

We studied the effects of two subanaesthetic concentrations of halothane (0.1 and 0.2 MAC) on the respiratory control system

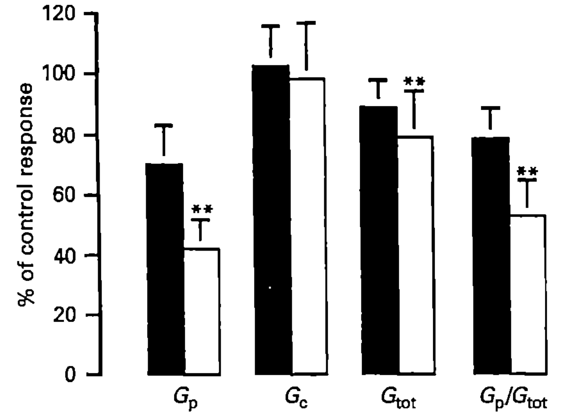

FIG. 3. Mean (SEM) carbon dioxide sensitivities after 0.1 MAC (■) and 0.2 MAC (□) of halothane. $^{**}P < 0.01$ compared with control.

and in particular on the peripheral chemoreflex loop using steps in $P\mathrm{E}'_{\mathrm{CO}_2}$. The study was approved by the local Ethics Committee and informed consent was obtained from all nine male subjects. The ventilatory responses were separated into a fast peripheral and a slow central dynamic component using a two-compartment model [1]. Each experiment started with 5-min baseline $\dot{V}\mathrm{I}$, followed by a stepwise increase in $P\mathrm{E}'_{\mathrm{CO}_2}$ (1.5 kPa) for 8 min. Thereafter, $P\mathrm{E}'_{\mathrm{CO}_2}$ was returned to its original value for another 8 min.

A total of 20 control, 18 0.1-MAC and 18 0.2-MAC halothane experiments were obtained. The peripheral carbon dioxide sensitivities (G_p) were mean 5.7 (SEM 1.1) (control), 3.8 (0.9) (0.1 MAC; ns) and 2.3 (0.6) litre min^{-1} kPa^{-1} (0.2 MAC; $P < 0.01$ *vs* control) (fig. 3). The central carbon dioxide sensitivities (G_c) and apnoeic thresholds did not differ among treatments. The ratios of G_p over total carbon dioxide sensitivity ($G_{tot} = G_p + G_c$) were 0.32 (0.06) (control), 0.24 (0.06) (0.1 MAC; ns) and 0.17 (0.05) (0.2 MAC; $P < 0.01$ *vs* control).

Our results indicate a significant depressant effect of 0.2 MAC of halothane on the peripheral chemoreflex loop but no effect on the central chemoreflex loop. We conclude that there was no effect on the respiratory centre in the CNS or on the neuromechanical link between brainstem and $\dot{V}\mathrm{I}$.

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CUFFED NASOPHARYNGEAL TUBE AND UPPER AIRWAY OBSTRUCTION

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Recent studies have emphasized different sites for upper airway obstruction under general anaesthesia [1]. A cuffed nasopharyngeal tube (CNPT), designed to be positioned beneath the soft palate [2], was considered to offer an opportunity for further investigation. Starting from the recommended position, the tube is withdrawn in stages, and the consequences for the airway assessed using fibreoptic laryngoscopy and monitoring respiration.

Ten patients (seven male) undergoing unilateral arthroscopy of the knee were studied. Nine were day-case patients. All were ASA I or II and suitable for nasal intubation. None was premedicated. In the anaesthetic room, fentanyl 75–100 µg was administered followed by propofol 170–200 mg. Increments of propofol were allowed until nasal intubation with CNPT was accomplished and respiration stabilized. Anaesthesia was maintained with nitrous oxide (67 %) and isoflurane (approximately 1 % end-tidal). CNPT position was checked by direct laryngoscopy. Head and neck position was standardized and monitored [3]. Respiration and vapour concentration were measured with a Datex Ultima. Recordings were made at five stages, each with four sets of observations. The first stage was with the CNPT positioned (behind the soft palate), the cuff inflated and the jaw pulled forward. Sets of observations (at each stage) noted consequences of any change in state and also effects of three "provocation" manoeuvres: jaw release, maximum neck flexion then both together. At the second stage, the cuff was deflated and a fibreoptic laryngoscope (FOL) was introduced into the remaining nostril. For this and the next two stages, the airway was visualized with the FOL. The third stage had the tip of the CNPT at the edge of the soft palate and in the fourth stage it was withdrawn into the nose. In the final stage, the FOL was also removed into the nose. Direct fibreoptic observations were thus possible for stages 2–4. Changes were defined as: partial obstruction—a decrease of tidal volume of 50 % or more; total obstruction—absence of monitored airflow (for 3–5 breaths, depending on ventilatory frequency).

In all cases a clear airway was obtained at the start of stage 1. In one case no obstruction was seen at all and in another changes were observed only with both provocation tests used together. In four of 10 patients, flexion produced partial or total obstruction with the CNPT in place and for three of these, the effect decreased as the tube was withdrawn. In the remaining patient, the airway was lost as soon as the CNPT cuff was deflated (so testing more distal sites was not possible). When the CNPT was withdrawn into the nose, two of nine patients had partial or complete obstruction on releasing the jaw. In one case the epiglottis produced complete obstruction after being "sucked down" over the laryngeal inlet.

This technique has limitations because only the most proximal cause of unprovoked total obstruction can be demonstrated. The FOL beneath the soft palate may itself cause a splinting effect, which is evident when it is withdrawn. This work clearly demonstrates that obstruction can occur at the epiglottis, the tongue or the soft palate, or combinations of these.

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PLASMA CONCENTRATION OF LIGNOCAINE AFTER NEBULIZATION FOR AWAKE FIBREOPTIC INTUBATION

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Awake fibreoptic intubation is a valuable procedure for the management of the difficult airway. Local anaesthetic techniques, such as translaryngeal injection or spray, are used to anaesthetize the airway. In the ophthalmic patient, nebulization using a 4% lignocaine solution has been used to reduce the pressor response to intubation [1]. The same technique can be used for awake fibreoptic intubation. However, a 4% solution requires a large volume of local anaesthetic and its absorption in patients who are undergoing head and neck surgery has not been studied. We therefore investigated the use of a 10% lignocaine solution in patients undergoing awake fibreoptic intubation.

After Ethics Committee approval and informed consent, 14 adult patients (six female) undergoing awake nasotracheal fibreoptic intubation were studied. Oral temazepam 10 mg and glycopyrronium 0.2 mg i.m. were given for premedication. Local anaesthesia for the upper airway comprised 4% topical cocaine spray to the nose (1.5 mg kg^{-1}) and nebulized 10% topical lignocaine (6 mg kg^{-1}) inhaled via an Acorn nebulizer. Once the airway was anaesthetized and intubated, a standard general anaesthetic was given. Blood samples were obtained for measurement of plasma concentration of lignocaine before and immediately after nebulization, and 10 and 20 min thereafter. Heart rate (HR) and systolic (SAP) and diastolic arterial pressure (DAP) were observed at similar times, as well as immediately after intubation.

Mean peak plasma concentration of lignocaine after nebulization was 1.51 (SD 1.1) µg ml^{-1}, decreasing to 0.95 (0.62) and 0.68 (0.32) µg ml^{-1} at 10 and 20 min, respectively. Immediately after nebulization, DAP showed a statistically significant but clinically unimportant increase (84.9 *vs* 90.6 mm Hg; $P < 0.05$). Mean SAP and DAP values 20 min after nebulization were significantly smaller than values immediately after nebulization (130.9 *vs* 148.4 and 80 *vs* 90.8 mm Hg, respectively; $P < 0.01$). Also, SAP at that time was significantly smaller than before nebulization (130.9 *vs* 149.5 mm Hg; $P < 0.01$).

Our earlier study [1] demonstrated that our technique of lignocaine nebulization produced stable haemodynamic responses to tracheal intubation. This study confirms these findings even in awake patients. However, peak plasma concentrations of lignocaine were greater in this group than in ophthalmic patients (1.51 (1.1) *vs* 1.07 (0.53) µg ml^{-1}).

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We would like to thank Astra Pharmaceuticals for their support of this study.

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ADMISSION BLOOD PRESSURE IS PREDICTIVE OF SILENT MYOCARDIAL ISCHAEMIA IN TREATED HYPERTENSION

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Perioperative silent myocardial ischaemia is predictive of adverse postoperative cardiac events in both vascular and non-vascular surgical populations [1]. An increase in arterial pressure at hospital admission has been shown to be associated with haemodynamic instability and ST segment depression during induction of anaesthesia and tracheal intubation [2]. As part of a wider study, we have investigated the predictive value of admission arterial pressure on perioperative silent ischaemia in the hypertensive population.

One hundred and thirty-one patients (79 male) more than 40 yr of age undergoing elective general or vascular surgical procedures gave informed consent to the study. Relevant history, examination findings and results of preoperative investigations were noted. A solid state ambulatory ECG recorder was fitted to record leads II and V5 before surgery (average duration 14 h 45 min (range 8 h 30 min to 24 h)). The recorder was re-attached in the recovery room and recordings continued over the first and second days after operation (average duration on first day after operation, 20 h and 30 min (8–24 h); average duration on second day after operation, 20 h and 30 min (13 h 30 min to 24 h)).

Arterial pressure at admission and all subsequent recordings were noted. Patients whose admission arterial pressure was less than 160/90 mm Hg were classified as normotensive or, if on treatment, as well controlled: patients whose admission arterial pressure was 160/90 mm Hg or greater were classified as untreated or as poorly controlled if on treatment. The choice of premedication, anaesthetic technique and postoperative monitoring and analgesic regimen were at the discretion of the individual anaesthetist. Statistical analysis of the data was carried out using the Student's t test and chi-square test.

Thirty-three patients were excluded because of 12-lead ECG abnormalities precluding accurate ST segment interpretation, recorder failure or patient withdrawal of consent. For the remaining patients, there were no differences between the four treatment groups with regard to patient age, male/female ratio or previous history of ischaemic heart disease. Patients with poorly treated hypertension had a 74% incidence of silent myocardial ischaemia ($\chi^2 = 13.615$; $P < 0.01$) (table II). There were no significant differences in the rates of silent myocardial ischaemia in the other patient groups.

Poorly treated hypertension detected by an increase in arterial pressure at admission is associated with a markedly increased risk of silent myocardial ischaemia. This may reflect a greater severity of disease in this group, compared with patients having a similar increase in arterial pressure on admission in the absence of treatment.

TABLE II. *Incidence of silent myocardial ischaemia (SMI) and sex distribution amongst the four patient groups*

Patient	Sex (M/F)	No. with SMI	Incidence SMI (%)
Normotensive ($n = 33$)	19/14	8	24
Well-treated ($n = 21$)	13/8	9	43
Poorly-treated ($n = 23$)	14/9	17	74
Untreated ($n = 21$)	16/5	9	43

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PREOPERATIVE OROLARYNGEAL LIGNOCAINE AND THE CARDIOVASCULAR PRESSOR RESPONSE TO LARYNGOSCOPY AND INTUBATION IN OPHTHALMIC PATIENTS

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Hypertension and tachycardia are known responses to laryngoscopy and intubation. They may be harmful in patients with existing cardiovascular disease. This pressor response results largely from laryngoscopy and is not always attenuated by topical spraying of the pharynx and larynx with lignocaine, when administered immediately before intubation [1]. In this study we compared the changes in cardiovascular variables when freon-free lignocaine was applied topically as either a direct pharyngolaryngeal–tracheal spray immediately before intubation or as an orolaryngeal spray before induction of anaesthesia.

Thirty consecutive patients, ASA I and II, undergoing routine ophthalmic operations were allocated randomly to one of two groups: group A received lignocaine 3 mg kg^{-1} (up to a maximum dose of 200 mg) as a direct pharyngolaryngeal–tracheal spray 1 min before intubation; group B received the same dose of an orolaryngeal spray of lignocaine on inspiration, in the sitting position, before induction of anaesthesia. The anaesthetic technique comprised oral diazepam 10 mg 2 h before operation, induction with thiopentone 3–5 mg kg^{-1}, atracurium 0.6 mg kg^{-1} and artificial ventilation with 65% nitrous oxide and 1% enflurane in oxygen via a Bain circuit. All patients were intubated by the same investigator (P.J.B.). Heart rate (HR) and systolic and diastolic arterial pressures (SAP and DAP) were recorded before induction, after orolaryngeal spray (group B), after induction, after intubation and 2.5 and 5 min after intubation. Data were analysed using paired and unpaired Student's t tests as appropriate.

There were no significant differences in patient characteristics between the two groups. One patient was withdrawn from group B and excluded from statistical analysis because of hypotension after induction. In both groups, induction and intubation significantly increased HR ($P < 0.05$ and $P < 0.001$, respectively). In group A, SAP decreased after induction ($P < 0.05$). Laryngoscopy and intubation significantly increased SAP ($P < 0.05$) and DAP ($P < 0.05$) compared with control and post-induction values. In group B there were no significant changes in response to the orolaryngeal spray. When compared with control values, DAP increased significantly in response to laryngoscopy and intubation ($P < 0.05$). Group A elicited a significantly greater

TABLE III. *Mean (SD) changes in HR, SAP and DAP recorded after orolaryngeal spray, after induction, after intubation and 2.5 min after intubation. Significant differences*: *P < *0.05*, ***P < *0.001 from baseline within groups*; †P < *0.05 between groups*

	Control	After spray	After induction	After intubation	+2.5 min
HR (beat min^{-1})					
Group A	75.4 (15.7)	—	84.7 (16.5)*	90.6 (12.4)***	80.9 (18.6)
Group B	71.3 (11.3)	75.5 (12.9)	80.6 (11.2)*	90.6 (15.6)***	77.5 (11.6)
SAP (mm Hg)					
Group A	154.6 (21.8)	—	136 (21)*	176.9 (34)*†	149 (27.8)
Group B	145.2 (21)	151 (32)	133.6 (22)	153 (25.3)	136 (24.6)
DAP (mm Hg)					
Group A	84.8 (11.5)	—	80.2 (15)	105 (24.4)*	89.3 (18.1)
Group B	82.9 (12.2)	89.9 (21)	75.5 (23)	96.3 (16.9)*	81.8 (13.5)

SAP ($P < 0.05$) at laryngoscopy and intubation compared with group B. In both groups, all variables were similar to control at 2.5 min (table III).

The application of freon-free lignocaine as an orolaryngeal spray before induction does not produce a pressor response. It is more effective than spraying immediately before intubation, but it does not fully ameliorate the pressor response to laryngoscopy and intubation.

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REGIONAL MYOCARDIAL ISCHAEMIA INCREASES STIFFNESS OF BOTH ISCHAEMIC AND NON-ISCHAEMIC MYOCARDIUM IN DOGS ANAESTHETIZED WITH FENTANYL

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Fentanyl produces minimal haemodynamic effects and is used widely as an anaesthetic or an anaesthetic supplement for patients undergoing cardiac surgery [1]. During halothane anaesthesia, regional myocardial ischaemia is associated with a two-fold increase in chamber stiffness of the ischaemic area and a 50% increase in chamber stiffness of the remote non-ischaemic myocardium [2]. The aim of this study was to determine the effects of myocardial ischaemia on regional left ventricular stiffness during fentanyl anaesthesia.

Eight mongrel dogs were instrumented to measure left ventricular pressure and circumferential segmental length (sonomicrometry) in ischaemic (left anterior descending coronary artery (LAD) supply) and non-ischaemic (left circumflex coronary artery supply) myocardium. After an initial loading dose of 100 $\mu g\ kg^{-1}$, fentanyl 2 $\mu g\ kg^{-1}\ min^{-1}$ was infused continuously and the animals' lungs were ventilated to normocapnia (40% oxygen in nitrogen). Blood (200 ml) was withdrawn and replaced by 5% Dextran. End-diastolic pressure–dimension relations were modified by stepwise (4×50-ml) infusion and withdrawal of this blood at baseline and during myocardial ischaemia (systolic bulging), which was applied by tightening of a snare around the LAD. Chamber stiffness was defined as the slope (k) of the exponential end-diastolic pressure(P)–length(L) relation: $P = e^{kL}$.

During fentanyl anaesthesia, regional myocardial ischaemia was associated with an increase in stiffness of both the ischaemic and the remote non-ischaemic myocardium (table IV). The degree of this increase in stiffness was similar to that observed during halothane anaesthesia [2]. Thus the changes in left ventricular stiffness brought about by myocardial ischaemia are not unique to a specific anaesthetic agent.

TABLE IV. *Effect of myocardial ischaemia on chamber stiffness (mean (SEM)) in ischaemic and non-ischaemic myocardium.* *P < *0.05* vs *baseline (Wilcoxon's signed rank sum test)*

	Baseline	Ischaemia
Ischaemic segment	0.55 (0.189)	0.95 (0.374)*
Non-ischaemic segment	1.18 (0.481)	1.55 (0.681)*

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CARDIOVASCULAR EFFECTS OF RECOMBINANT HUMAN HAEMOGLOBIN (rHb1.1) IN A CANINE MODEL OF NORMOVOLAEMIC HAEMODILUTION

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A safe, haemoglobin-based oxygen carrier (HBOC) blood substitute has been sought for over 50 years. The renal toxicity of stroma-free haemoglobins can be overcome by stabilizing the haemoglobin tetramer. However, significant systemic and pulmonary vasoconstriction has been reported with infusions of HBOC [1]. Therefore, we studied the cardiovascular effects of recombinant human haemoglobin (rHb1.1), genetically engineered, stabilized HBOC [2], in a canine model of normovolaemic haemodilution (approximately 50% blood volume exchange).

Fourteen mongrel dogs (weights 20–23 kg) were anaesthetized with halothane (0.9% end-tidal) and underwent a left thoracotomy. The animals were instrumented so as to measure the following: left and right ventricular, aortic and pulmonary pressures (micromanometer-tipped catheters); aortic and left anterior descending coronary artery (LAD) flow (Doppler ultrasonography); regional myocardial function in the anterior and posterior apical left ventricle and the right ventricular mid-wall (sonomicrometry); arterial, pulmonary arterial and LAD-supplied myocardial venous oxygen saturation and haemoglobin content; arterial PCV and blood volume (^{51}Cr labelled RBC). Dogs were allocated randomly after surgical preparation to receive 40 $ml\ kg^{-1}$ (2 $g\ kg^{-1}$) of 5% rHb1.1 or human serum albumin (HSA) as a constant infusion over 1 h. Arterial blood was

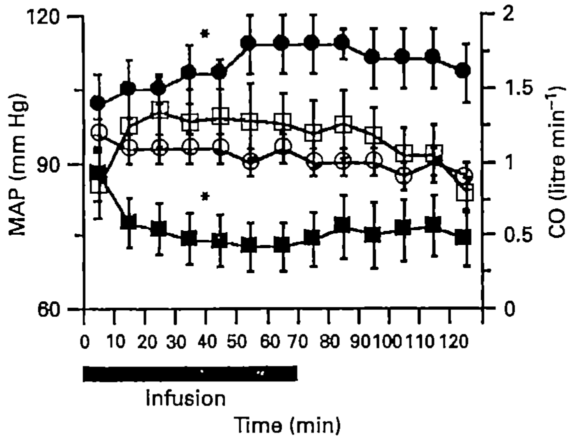

FIG. 4. Comparison of changes in mean arterial pressure (MAP) (■, □) and cardiac output (CO) (●, ○) between rHb1.1 (open symbols) and HSA (filled symbols) groups. *$P < 0.05$ between rHb1.1 and HSA groups.

simultaneously withdrawn during infusion such that the ratio of infusion to withdrawal was 1.1. Haemodynamic data and blood samples were recorded every 10 min during the 1-h infusion and for 1 h thereafter. The responses to rHb1.1 were compared to HSA by ANOVA for repeated measures. Data are presented as mean (SEM).

All animals survived the 2 h study. PCV and blood volumes were identical in the two groups after haemodilution. There were statistically significant ($P < 0.05$) differences in cardiac output (CO), mean arterial pressure (MAP) (fig. 4) and systemic vascular resistance (SVR) between rHb1.1 and HSA groups during and after haemodilution. MAP and SVR increased and CO decreased during the first 20 min of haemodilution with rHb1.1 and then remained stable for the duration of the study. Compared to baseline values, the average maximal changes observed after rHb1.1 were: CO −18% (at 120 min), MAP +19% (at 20 min), SVR +53% (at 50 min). No significant differences between the two groups were noted in pulmonary arterial pressures, global ventricular measures of contractility (LV dP/dt, RV dP/dt) or in regional myocardial function. Left ventricular end-diastolic pressure remained constant throughout the study in both groups and measured blood volumes at the end (2 h) of the study were within 15% of baseline blood volumes.

This study revealed no significant adverse cardiovascular effects of rHb1.1 during or after 50% normovolaemic haemodilution in halothane-anaesthetized dogs. The modest increase in MAP was secondary to peripheral effects (increased SVR), and a slight decrease in CO occurred in the rHb1.1 group compared with HSA. In this model, rHb1.1 did not effect global or regional myocardial contractility or cause pulmonary hypertension. These data support the cardiovascular safety of rHb1.1 as an oxygen carrier for use in perioperative blood replacement.

ACKNOWLEDGEMENT

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EFFECT OF THIOPENTONE AND OPIOIDS ON FERTILIZATION AND EMBRYO DEVELOPMENT IN THE MOUSE

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A longer duration of anaesthesia exposure during laparoscopic retrieval of oocytes for *in vitro* fertilization (IVF) has been correlated with lower cleavage rates [1]. As thiopentone and fentanyl attained appreciable concentrations in the follicular fluid after i.v. bolus injection [2, 3], we decided to determine the effect of clinical concentrations of thiopentone, fentanyl, pethidine and morphine on mouse IVF and early embryonic development of two-cell embryos.

For IVF, sperm were obtained from the epididymes of two (CBA♂ × C57♀) F1 hybrid male mice and oocytes from the oviducts of superovulated females. Oocytes were exposed to media containing fentanyl 1 ng ml^{-1}, morphine 20 ng ml^{-1}, pethidine 100 ng ml^{-1} and thiopentone 4 μg ml for 30 min and control samples contained plain media (Whittingham's T6 with bovine serum albumin supplementation). The concentrations of the drugs were similar to plasma concentrations obtained after i.v. injection of clinical doses of these drugs. The oocytes were then inseminated for 4 h after which they were transferred to fresh media for culture for the next 120 h.

In the second experiment, two-cell embryos obtained from the oviducts of mated females were exposed to the anaesthetic drugs for 30 min as described above. They were then cultured for 72 h. Six replicates were performed in each experiment.

There were no significant differences (ANOVA) between fertilization (percentage of oocytes developing to the two-cell stage at 24 h after insemination) and blastocyst rates (percentage of two-cell embryos developing to expanded blastocysts at 72 h after culture) in all the groups (table V). In addition, there were no differences between other stages of cleavage (eight-cell, early and hatching blastocysts) of the two-cell embryos.

This study showed that clinical concentrations of thiopentone, fentanyl, pethidine and morphine had no deleterious effects on fertilization and early embryonic development in the mouse.

TABLE V. *Mean* (SEM) *fertilization rate of oocytes and blastocyst rate of two-cell embryos* [n *pooled from six replicates in each experiment*]. *There were no significant differences* (*ANOVA*) *between all five groups*

Group	Fertilization rate (%)	Blastocyst rate (%)
Control	68.8 (2.2) [266]	89.8 (2.9) [239]
Fentanyl	73.1 (4.9) [240]	83.8 (4.4) [249]
Pethidine	72.4 (5.2) [253]	90.8 (2.3) [226]
Morphine	73.4 (2.7) [225]	82.4 (2.9) [237]
Thiopentone	73.4 (3.4) [270]	87.0 (2.9) [248]

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EFFECT OF MORPHINE AND CLONIDINE ON NEUROPEPTIDE AND GENE EXPRESSION IN THE SPINAL CORD IN A MONONEUROPATHIC RAT MODEL

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Bennett and Xie [1] described an animal model of mononeuropathy induced by ligation of the sciatic nerve, which displays many of the features of neuropathic pain, including hyperalgesia and allodynia. In our study, either saline, morphine 5 mg kg^{-1} or clonidine 1 mg kg^{-1} was given i.p. 30 min before and 6 h after the ligation or sham operation which was performed under isoflurane anaesthesia. For the sham operation, the sciatic nerve was exposed, but not manipulated. Animals received ligation or sham operation in one limb only, in both cases the contralateral limb remained unoperated. The survival time was 28 days, at which point both

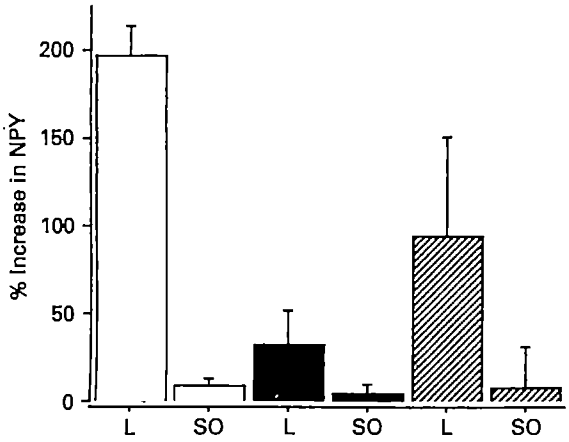

FIG. 5. Mean (SEM) percentage increase in neuropeptide Y (NPY) in layer III of the dorsal horn in response to saline □, morphine (■) or clonidine (■) after ligation (L) or sham operation (SO).

ipsilateral and contralateral paw withdrawal thresholds were measured with an "Algesymeter". The animals were then killed and quantitative fluorescent immunohistochemistry was used to analyse the L4–5 spinal cord. Eighteen ($n = 3$ per group) animals have so far been included in the study. Data were analysed using ANOVA and the Bonferroni–Dunn procedure.

Ligated animals were hyperalgesic compared to shams and treatment with either morphine ($P = 0.001$) or clonidine ($P = 0.001$) suppressed the behavioural hyperalgesia response compared to the saline group. Sham animals showed no change. In all cases measurements were compared to the contralateral (unoperated) side of the spinal cord. Ligated animals showed decreased ipsilateral Isolectin IB4 staining of sciatic nerve territory of the superficial dorsal horn. The levels of calcitonin gene related peptide (CGRP) and substance P decreased ipsilaterally in the superficial dorsal horn whilst the area of galanin staining increased in the superficial dorsal horn. Dynorphin staining increased ipsilaterally in the deep dorsal horn. The sham animals showed similar changes but of significantly smaller magnitude ($P < 0.0001$). The immediate early gene proteins Fos and Jun were at basal values in all animals. The peptide and gene changes so far described were not affected by drug treatment. However neuropeptide Y showed a different response pattern. Neuropeptide Y increased in [illegible] III of the dorsal horn in response to ligation but treatment [illegible] morphine ($P = 0.003$) and possibly clonidine ($P = 0.03$) suppressed this increase in neuropeptide Y (fig. 5).

Unlike CGRP, substance P and galanin, which simply reflect the extent of the nerve lesion, the changes in neuropeptide Y reflected the behavioural responses of the animal in response to drug treatment. The increase in neuropeptide Y may represent part of the adaptive response of the nervous system and may be open to further pharmacological intervention.

ACKNOWLEDGEMENT

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NO BASIS FOR CHARACTERIZING MALIGNANT HYPERTHERMIA SUSCEPTIBLE PATIENTS BY FLUORESCENCE MEASUREMENTS OF CALCIUM ION CHANGES IN NEUTROPHILS

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There is controversy as to the use of cytoplasmic calcium ion concentrations $[Ca^{2+}]_i$ in neutrophils and the magnitude of change in these upon the addition of halothane for the diagnosis of malignant hyperthermia susceptibility (MHS) [1, 2]. This study is a further examination of the techniques involved.

Patients attending for diagnostic muscle biopsy were typed according to the European MH group procedure [3]. At the time of biopsy, 10 ml of venous blood was collected into heparinized containers from the starved patients and then diluted with HEPES buffered RPMI 1640 culture medium 10 ml. The neutrophils were separated by gradient centrifugation on Histopaque 1077 and then loaded with fura-2 by incubating with fura-2AM for 60 min at 37 °C. After washing twice, the neutrophils were resuspended in 2 ml of HEPES buffered saline containing EGTA and no calcium and placed in a cuvette in a Perkin–Elmer LS50 luminescence spectrofluorimeter with a constant stirring facility. $[Ca^{2+}]_i$ was determined from the ratio of emission intensity at 510 nm at excitation frequencies of 340 nm and 380 nm and a calibration procedure utilizing maximum and minimum intensities obtained with inonmycin and manganese ions, respectively. Readings were made in the absence of extracellular calcium, after the addition of $CaCl_2$ 1 mmol litre^{-1} and after the further addition of halothane 0.44 mmol litre^{-1}.

We encountered several technical problems which could not be anticipated from the previous studies, especially the amount of noise from the signal. Figure 6 summarizes the $[Ca^{2+}]_i$ changes in the MHS and malignant hyperthermia negative (MHN) patients after addition of halothane.

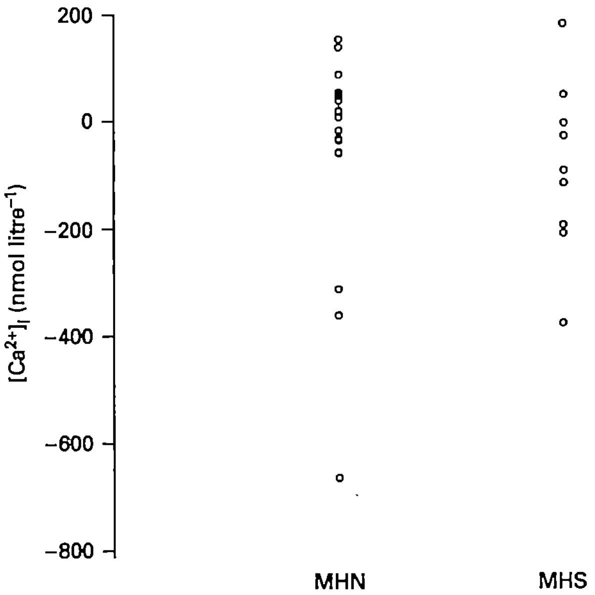

FIG. 6. Changes in calcium ion concentration $[Ca^{2+}]_i$ in malignant hyperthermia susceptible (MHS) and negative (MHN) patients after addition of halothane.

The measurement of $[Ca^{2+}]_i$ using these methods is not straightforward; we are still investigating possible explanations for the technical problems we encountered. Our results provide no basis for the use of intracellular calcium responses of neutrophils to halothane in the diagnosis of MHS.

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COMPARISON OF THE EFFECTS OF ISOFLURANE AND PROPOFOL ON HEPATIC GLUTATHIONE-S-TRANSFERASE ACTIVITY DURING AND AFTER PROLONGED ANAESTHESIA

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Hepatic glutathione-S-transferase (GST) is a superior marker of hepatocellular damage after halothane anaesthesia compared with aminotransferases [1, 2]. The hepatic effects of prolonged propofol infusions during reconstructive surgery have not been studied.

Twenty patients undergoing prolonged plastic and reconstructive surgery (approximately 10 h) received either propofol (group 1; $n = 10$) or isoflurane (group 2; $n = 10$) anaesthesia by random allocation. Ethics Committee approval and informed consent were obtained. Premedication was with oral lorazepam 2–4 mg, 60–90 min before surgery. Group 1 received an initial bolus dose of alfentanil 30 µg kg^{-1} followed by an infusion at 30–50 µg kg^{-1} h^{-1}. Anaesthesia was induced with propofol 2.0 mg kg^{-1} and atracurium 0.5 mg kg^{-1} and maintained with propofol by infusion at 10 mg kg^{-1} h^{-1} for 10 min followed by 8 and 6 mg kg^{-1} h^{-1} at 10-min intervals. Thereafter the rate of propofol was adjusted to the clinical haemodynamic response. Group 2 received alfentanil and atracurium as before but anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and maintained with isoflurane at an end-tidal concentration of 1–2% (Datex, Normocap). Normocapnic IPPV was maintained with oxygen-enriched air ($F_{I_{O_2}}$ 0.4). Blood samples for GST estimations were obtained at 2, 4, 6, 8, 10, 24 and 48 h and at seven days. Results were subjected to ANOVA. Inter- and intra-assay coefficients of variance for GST analysis ranged between 5 and 17%.

Patient characteristics were similar in the two groups. Mean (SD) duration of surgery was 11.3 (1.33) h (group 1) and 10 (1.1) h (group 2) ($P > 0.05$). Mean plasma GST activity did not exceed the normal range in any sample from any patient. Although GST concentrations in the propofol group were smaller than those in the isoflurane group, these differences were not statistically significant (table VI).

Prolonged anaesthesia with propofol or isoflurane has no statistically significant effect on plasma GST activity either during or after extended reconstructive surgery.

TABLE VI. *Mean* (SD) *GST activity* (*µg litre*$^{-1}$) *during and after prolonged propofol or isoflurane anaesthesia*

	Propofol	Isoflurane
Baseline	3.8 (2.7)	7.6 (6.5)
2 h	7.7 (1.3)	7.3 (4.6)
4 h	3.8 (1.8)	6.6 (2.6)
6 h	5.3 (1.2)	7.1 (5.1)
8 h	3.1 (2.0)	6.0 (4.7)
10 h	2.6 (2.2)	5.1 (3.9)
24 h	2.0 (2.1)	4.0 (3.4)
48 h	2.6 (1.1)	2.1 (1.1)
7 days	3.3 (1.7)	6.5 (4.2)
Normal range	0.5–10.0	

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IN VITRO METABOLISM OF THE *CIS-CIS* ISOMER OF MIVACURIUM

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The *cis-cis* isomer of mivacurium (6% of the solution) has been shown to have a considerably longer half life *in vivo* than the *cis-trans* and *trans-trans* isomers, and in contrast, no clear relationship between its clearance and plasma cholinesterase activity has been demonstrated [1, 2]. It was therefore decided to investigate the metabolism of this isomer *in vitro*.

An expired unit of whole blood was obtained from the Blood Transfusion Service, the plasma separated and its cholinesterase activity determined [1]. The plasma was then used in seven experiments, each performed in duplicate. In each instance, the plasma was incubated at 37 °C and maintained at pH 7.4 with phosphate buffer. The seven tubes contained: (i) plasma 10 ml, (ii) plasma 5 ml + phosphate buffer 5 ml, (iii) plasma 2.5 ml + phosphate buffer 7.5 ml, (iv) phosphate buffer 10 ml, (v) plasma 10 ml + neostigmine 500 ng ml^{-1}, (vi) plasma 10 ml + edrophonium 5000 ng ml^{-1} and (vii) plasma 10 ml + phospholine iodide 0.1 mg ml^{-1}. All tubes were mixed well and cholinesterase inhibitors were allowed to incubate for at least 10 min before the addition of mivacurium. At time 0, *cis-cis* mivacurium (U1217 U84) was added to each tube to achieve a concentration of 1500 ng ml^{-1}. Each tube was agitated to ensure thorough mixing. Plasma samples (1 ml) were taken at 5, 30, 60, 120, 180, 240 and 300 min, and added immediately to tubes containing phospholine iodide 0.5 mg. Samples were then extracted and analysed using an HPLC technique with d-tubocurarine as an internal standard. The coefficient of variation of the assay was 12% and the sensitivity 10 ng ml^{-1}. The k_{el} for each experiment was calculated by log–linear regression and the half-time derived ($T_{\frac{1}{2}} = 0.693/k_{el}$). The clearance that might be expected from plasma cholinesterase activity alone, assuming a 70-kg individual with a plasma volume of 3500 ml, is presented.

Plasma cholinesterase activity was 1033 iu litre^{-1} (normal range 620–1370 iu litre^{-1}), the dibucaine and fluoride numbers were normal. Half-times and derived clearance values of *cis-cis* mivacurium are shown in table VII.

The half-time of *cis-cis* mivacurium is longer than that of the other isomers *in vivo*, thus its route of elimination is of interest. This study demonstrates that it is metabolized *in vitro* by plasma cholinesterase, although extrapolated clearance values are a factor of 10 smaller than those determined from *in vivo* studies [1, 2], implying some other route of elimination for this isomer *in vivo*. *In vitro* metabolism is inhibited by phospholine iodide and by neostigmine at a clinically relevant concentration, but not by edrophonium.

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TABLE VII. *Half-times* (*95% confidence intervals*) *and derived clearance values of* cis-cis *mivacurium.* **Cholinesterase activity was 1033 iu litre*$^{-1}$

Sample	$T_{\frac{1}{2}}$ (min)	*Cl* (ml kg^{-1} min^{-1})
Plasma 10 ml*	89 (82–96)	0.39
Plasma 5 ml + buffer 5 ml	108 (96–122)	0.32
Plasma 2.5 ml + buffer 7.5 ml	139 (119–165)	0.25
Buffer 10 ml	673 (433–1575)	0.05
Plasma 10 ml + neostigmine 500 ng ml^{-1}	840 (471–3829)	0.04
Plasma 10 ml + edrophonium 5000 ng ml^{-1}	115 (104–129)	0.30
Plasma 10 ml + phospholine iodide 1 mg	989 (529–7787)	0.04

SYSTEMIC CLEARANCE AND THE ONSET OF NON-DEPOLARIZING NEUROMUSCULAR BLOCK

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The finding [1] of an inverse relationship between the size of the i.v. dose of a neuromuscular blocking agent needed to produce 90% neuromuscular block and (i) the onset time to 50% neuromuscular block, (ii) the duration of neuromuscular block and (iii) the recovery index, has generated much interest. Theoretical explanation [2] for the fast onset *vs* low potency relationship does not account for the other two findings, that is that the neuromuscular block produced by a less potent neuromuscular blocker (large ED_{90}) is of short duration and recovers quickly. As an alternative to the proposed explanation, I tested the hypothesis that the pharmacokinetic properties of the neuromuscular blockers determine the onset of the neuromuscular block.

The concentration of a neuromuscular blocker at the receptors on the motor end-plate was approximated by its concentration in the interstitial space of the muscle. In turn, the filling and emptying of this space were simulated as dependent on the plasma concentration of the neuromuscular blocker according to the flow–volume model [3]. Pharmacokinetic properties of 500 neuromuscular blockers were defined by the common values for V_C and V^{ss} (0.1 and 0.25 litre kg^{-1}, respectively) and varying values for systemic clearance, Cl_{sys} (0.1–60 ml kg^{-1} min^{-1}), and the volume of distribution during the elimination phase, V_{area} (0.275–0.5 litre kg^{-1}). The concentration of a neuromuscular blocker in the interstitial space of the muscle was characterized by the time (min) to peak concentration and the magnitude of the peak concentration relative to the initial concentration in plasma. All neuromuscular blockers were assumed to have identical concentration *vs* neuromuscular block relationship (i.e. to have common EC_{50} and γ values).

The results revealed that, after equimolar doses, neuromuscular blockers with large Cl_{sys} values achieve an early concentration in the interstitial space of the muscle. The influence of V_{area} was less marked. However, an early peak concentration in the interstitial space was associated with smaller peak concentration in the interstitial space. Equal concentrations in the interstitial space were achieved for all neuromuscular blockers by increasing the bolus i.v. doses of those neuromuscular blockers that produce early but small peak concentrations in the interstitial space. We postulated that this peak concentration represents EC_{90} values for all neuromuscular blockers. By definition then, the peak neuromuscular block is 90% for all neuromuscular blockers and the dose of each neuromuscular blocker represents its ED_{90}. The plots of: (i) the time to peak concentration in the interstitial space of the muscle (= time to 90% neuromuscular block), (ii) the time for the neuromuscular block to decrease to 50%, and (iii) the recovery index, against ED_{90} displayed the same relationship that was found experimentally.

I conclude that it is not necessary to postulate a correlation between the fast onset of the neuromuscular block and the low potency of a neuromuscular blocker. All experimental findings are well accounted for by assuming that a large value for ED_{90} in a series of chemically related neuromuscular blockers results from greater Cl_{sys} values. Therefore, the large value for Cl_{sys} favours a fast onset of neuromuscular block independent of the potency of the blocker in terms of EC_{50}.

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REVERSAL OF ROCURONIUM BLOCK WITH EDROPHONIUM OR NEOSTIGMINE

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Rocuronium (Org 9426) is a desacetoxy derivative of vecuronium with a relatively fast onset and intermediate duration of action [1]. In the present study, we have examined the recovery of rocuronium-induced neuromuscular block with or without anticholinesterase administration.

Fifty patients were included in the study after informed consent and Ethics Committee approval. Patients were premedicated with temazepam and anaesthetized with fentanyl 2–3 μg kg^{-1}, thiopentone 4–5 mg kg^{-1} and nitrous oxide and 0.75% halothane in oxygen. Neuromuscular monitoring was by stimulation of the ulnar nerve at the wrist with supramaximal stimuli of 0.2-ms duration in a train-of-four (TOF) mode every 12 s and recording of the force of contraction of the adductor pollicis muscle. After stabilization of the control responses, patients were given rocuronium 0.45 mg kg^{-1} and the trachea intubated when maximum block had supervened. An infusion of rocuronium was commenced at 10% recovery of T1 (first response of TOF) and the rate of infusion changed as required to maintain T1 at about 10%. At the end of surgery, 10 patients each were allocated randomly to either spontaneous recovery (group S) or antagonism of block at a T1 height of 10% or 25% with edrophonium 1 mg kg^{-1} (groups E10 and E25) or neostigmine 0.05 mg kg^{-1} (groups N10 and N25). Neuromuscular recording was continued for the next 10 min and various indices of recovery recorded. The results were subjected to analysis of variance.

The results are shown in table VIII. Recovery in patients not receiving the anticholinesterases was significantly slower compared to the other groups. The onset of action was shorter with edrophonium but the difference was significant only between groups N10 and E10. Recovery in general was faster when the antagonist was given at recovery of T1 to 25%. The most rapid attainment of TOF ratio of 0.7 was in group E25 and the slowest in group E10. One patient each in groups S and N25 and three in group E10 failed to attain a TOF ratio of 0.7.

TABLE VIII. *Mean* (SD) *times to onset of action of antagonism and to attaining T1 of 90% and TOF ratio of 0.7. Significant differences*: *P < *0.05 compared with group E10*; †P < *0.05 compared with group E25*; ‡P < *0.05 compared with groups N10 and E10*

Group	*n*	Times to Onset (s)	 T1 = 90% (min)	 TOF = 0.7 (min)
S	10	—	31.4 (11.7)	36.1 (7.3) (*n* = 9)
N10	10	49.6 (6.9)*	7.9 (4.7)† (*n* = 8)	7.5 (1.9)
E10	10	36.3 (9.5)	4.1 (3.7)	9.3 (7.0) (*n* = 7)
N25	10	43.2 (9.5)	4.1 (2.3)	4.6 (1.9) (*n* = 9)
E25	10	40.7 (11.7)	2.1 (2.1)	1.9 (0.9)‡

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EFFECT OF INDUCTION OF ANAESTHESIA WITH PROPOFOL ON SUXAMETHONIUM-INDUCED MYALGIA

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Suxamethonium-induced myalgia is common [1] and a wide variety of techniques have been used to reduce its incidence and severity [2]. The clinical observation that intubation can be performed under propofol alone [3] suggests that it causes some neuromuscular block. This study investigated if induction of anaesthesia with propofol had any influence on suxamethonium-induced myalgia.

Sixty adult patients undergoing extraction of wisdom teeth under general anaesthesia were randomized to one of three groups. Group 1 and 2 patients were anaesthetized with

TABLE IX. *Median (range) pain scores using VAS scores for suxamethonium-induced myalgia.* *P < *0.05 compared with group 1*

	0 h	24 h	48 h	72 h
Group 1	0.0 (0–4.5)	4.15 (0–10)	2.6 (0–9.8)	0.0 (0–3.0)
Group 2	0.0 (0–6.5)	1.0* (0–9.6)	0.0* (0–8.4)	0.0 (0–3.2)
Group 3	0.0 (0–6.8)	0.35* (0–8.1)	0.0* (0–10)	0.0 (0–1.2)

thiopentone 4–5 mg kg^{-1} by i.v. injection whilst group 3 received propofol 2.5 mg kg^{-1}. Suxamethonium 1.5 mg kg^{-1} was given i.v. and the trachea intubated nasally under direct vision. Group 2 patients received gallamine 0.2 mg kg^{-1} i.v. 2 min before induction. Anaesthesia was maintained with 67 % nitrous oxide in oxygen supplemented with 1–3 % enflurane as required. Patients were asked to complete a visual analogue scales (VAS) for muscle pains after operation and to indicate diagramatically the position of their pain. The patients were asked to score their muscle pain on four occasions: immediately on returning to the ward from surgery (time 0), at 24, 48 and 72 h after operation. Statistical analysis was performed using Kruskal–Wallis and Mann–Whitney tests.

There were no significant differences in pain scores between the groups at 0 and 72 h (table IX). However, there were significant differences in pain scores at 24 and 48 h between both groups 2 and 3 and group 1, although there was no difference when group 2 was compared to group 3. We conclude that induction of anaesthesia with propofol is as effective at reducing suxamethonium-induced myalgia as gallamine pretreatment.

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NEUROMUSCULAR EFFECTS OF ENFLURANE IN MYASTHENIA GRAVIS

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Train-of-four (TOF) fade is often found in sufferers of myasthenia gravis. Both TOF fade and tetanic fade are believed to reflect reduced acetylcholine output [1], a process which volatile anaesthetics inhibit [2]. We studied these and other indices of neuromuscular function in myasthenics at varying concentrations of enflurane.

Three acetylcholine receptor–antibody positive patients undergoing thymectomy were enrolled in this IRB-approved study. All were receiving pyridostigmine medication which had been stopped 12–15 h before surgery. One hour after premedication with papaveretum 0.25 mg kg^{-1} and scopolamine 5 µg kg^{-1}, anaesthesia was induced with propofol 2 mg kg^{-1} and fentanyl 1.5 µg kg^{-1}, nasal intubation performed and the lungs ventilated with 66 % nitrous oxide in oxygen to a $P\mathrm{E}_{\mathrm{CO_2}}$ of 4 kPa. Supramaximal stimulation of the ulnar nerves at the wrists was elicited at 0.2 Hz, the resulting adductor pollicis twitch of both arms measured by RS2 load cells and recorded. Anaesthesia was maintained by propofol infusion, which was proportionately reduced as enflurane was added to the inspired gas once stable twitch height had been achieved. After 5–10 min of stabilization at a chosen end-tidal enflurane concentration (measured by a Datex infrared analyser) a 5-s, 50-Hz tetanus was applied to one arm whilst 2-Hz TOF stimulation was given to the other. The TOF and tetanic fade ratios were measured together with tetanic power, the integral of the 5-s tension response [3]. The maximal end-tidal enflurane concentrations achieved in patients 1, 2 and 3 were 2.5, 1.5 and 2.0 %, respectively. At maximal concentration, patient 1 received edrophonium 0.16 mg kg^{-1} and patient 3 was given neostigmine 0.05 mg kg^{-1}. The results are shown in table X.

Tetanic power was the most sensitive index and may be a useful monitor of neuromuscular function [3]. TOF and TF appeared to differ in their response to enflurane and anticholinesterase.

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TABLE X. *Measured indices for the three patients at zero and maximal (Max.) enflurane concentrations. TF = Tetanic fade (%); TP = tetanic power (%); E/N = maximum response after anticholinesterase*

	Patient 1			Patient 2			Patient 3		
	TF	TOF	TP	TF	TOF	TP	TF	TOF	TP
Control	86	100	100	85	96	100	93	90	100
Max.	75	62	35	71	36	16	93	67	47
E/N	70	87	44	—	—	—	91	88	105

PHARMACOKINETICS OF *CIS-CIS* MIVACURIUM: A POPULATION APPROACH

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A solution of mivacurium contains these stereoisomers, *trans-trans* (57 %), *cis-trans* (37 %) and *cis-cis* (6 %). The two more abundant isomers are rapidly metabolized by plasma cholinesterase: the clearance of the *cis-cis* isomer is less than 10 % of the other two isomers [1]. We present the pharmacokinetics of *cis-cis* mivacurium in a series of 25 patients. The aim was to define a pharmacokinetic model for this isomer and to test the effects of certain within-population variables upon its disposition.

Data from two studies [1, 2] were combined to yield pharmacokinetic data from 25 anaesthetized patients. Five healthy patients received mivacurium 150 µg kg^{-1} by infusion over 10 min. The remaining 20 patients received mivacurium 150 µg kg^{-1} over 10 min followed by 75 µg kg^{-1} over 10 min, and then an infusion at a variable rate to maintain depression of the first response of the train-of-four (T1 : T0) at 5 %. Of these 20 patients, eight were healthy, seven were in renal failure requiring dialysis (creatinine clearance 0–11 ml min^{-1}) and five had an intermediate degree of renal function (creatinine clearance 39–63 ml min^{-1}). The five patients with intermediate renal function all had a functional renal transplant and were receiving immunosuppressive medication, including cyclosporin 300–600 mg daily, azathioprine 0–100 mg daily and prednisolone 0–20 mg daily.

Pharmacokinetic models were fitted using double precision NONMEM v4, level 1.1, compiled by Salford Fortran FTN77, and run on an IBM compatible microcomputer. One- and two-compartment models could be fitted using ADVAN1 and ADVAN3 options of the NONMEM extension, PREDPP. Multiplicative error models and first-order estimation methods were used throughout. Statistical comparisons were made of maximum log likelihoods (the NONMEM objective function (O.F.)) and model development guided by scatterplots [3].

Patients were aged 17–64 yr and weighed 40–85 kg; 13 were male, 12 were female. Plasma cholinesterase ranged from 373 to 1280 iu litre^{-1}: 463 data points were available for analysis.

TABLE XI. *Mean population pharmacokinetic model together with standard errors* (SE) *of the estimate, and estimations of population variability* (*expressed as coefficient of variation* (*cv*))

	Mean	SE	Popn cv (%)
Cl (ml min^{-1} kg^{-1})	3.18	0.31	38
V (ml kg^{-1})	79.5	12.2	35
V^{ss} (ml kg^{-1})	288	20.4	31
Intercompartmental *Cl* (ml min^{-1})	395	84.7	37

A two-compartment model was preferred to a single compartment model (O.F. difference = 907). The mean population pharmacokinetic model and estimates of population variability (expressed as coefficient of variation) are shown in table XI. Significant effects on clearance were found for creatinine clearance (O.F. difference = 5.5; $P < 0.025$), intermediate renal function (O.F. difference = 56.1; $P < 0.001$) and cholinesterase activity (O.F. difference = 23.9; $P < 0.001$).

A population approach provides evidence for elimination of *cis-cis* mivacurium by cholinesterase, by renal function, and by a third mechanism which is affected in the intermediate renal function group.

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FUNCTIONAL MRI OF KETAMINE-INDUCED CHANGES IN rCBF: AN EFFECT AT THE NMDA RECEPTOR?

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The changes in signal intensity on long TE **GR**adient **E**cho (GRE) sequences produced by neuronal activation are believed to be a result of reduction in the regional concentrations of deoxyhaemoglobin caused by increases in regional cerebral blood flow (rCBF) that exceed the increase in local oxygen requirements [1]. Ketamine at low doses has been shown to produce autoradiographic increases in regional cerebral glucose utilization in the hippocampus, cerebral cortex and olfactory region [2]. However, autoradiographic techniques may be cumbersome when dynamic changes are being studied. This study shows that functional MRI with GRE can be used to study changes in rCBF produced by ketamine in a rat model and compares these changes with those produced by the NMDA antagonist dizocilpine (MK-801).

Rats were anaesthetized using either 1 % halothane in oxygen or a fentanyl–fluanisone–midazolam combination. Imagining was performed using a 60-ms TE GRE with a repetition time of 1500 ms and two signal averages, on a 2.35 T horizontal bore system. After baseline images were obtained, ketamine was delivered either as a 10 mg kg^{-1} bolus or as a pharmacokinetically modelled low-dose infusion [2] and imagining recommenced. Further animals were imaged after dizocilpine 0.5 mg kg^{-1}.

In rats anaesthetized with the fentanyl–fluanisone–midazolam combination, images acquired during the redistribution phase after a bolus injection of ketamine 10 mg kg^{-1} showed a transient increase in signal in the hippocampus, cortex and olfactory cortex of 14–20 %, while the rest of the brain and surrounding tissue showed no significant changes in signal intensity. Marked increases in signal intensity were also seen in the posterior part of the eye. Similar but more sustained changes in signal intensity were seen with low-dose ketamine infusion. These changes were less prominent and less consistent when basal anaesthesia was maintained with halothane. The patterns of increase in signal intensity correspond to previous autoradiographic studies of changes in rCBF with ketamine. In the animals that received dizocilpine, we observed patterns of rCBF change similar to those seen with low-dose ketamine.

These results agree well with autoradiographic studies of regional glucose uptake in the literature. Quantitative measurements of changes in rCBF will require quantification of susceptibility changes in blood at 2.35 T as a function of oxygen saturation or calibration against other techniques, such as hydrogen clearance or autoradiography. Preliminary results using dizocilpine show similar changes in rCBF, supporting the suggestion that ketamine may produce its effects via the NMDA receptor [2]. The less consistent responses obtained in animals anaesthetized with halothane are in keeping with the ability of this agent to disrupt the increased regional cerebral glucose uptake normally seen with NMDA receptor antagonists [3].

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STATISTICAL SIGNIFICANCE MAY NOT MEAN CLINICAL IMPORTANCE

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A total of 116 patients were anaesthetized with one of four anaesthetic techniques during the course of other studies presented to the society. An attempt was made to determine any relationship between patient characteristics, observations in theatre and the time to recovery from the anaesthetic.

All patients were aged 18–25 yr, ASA I, presenting for day-case dental surgery and had been allocated randomly to one of four anaesthetic techniques described previously [1]. These were spontaneous respiration with 1.5–2 % isoflurane, spontaneous respiration with propofol–alfentanil infusion 15/12/9 mg kg h^{-1}, ventilation with 0.5 % isoflurane and ventilation with propofol–alfentanil infusion 7.5/6/4.5 mg kg h^{-1}.

Age, weight, sex, induction–incision time, duration of anaesthesia and time from end of surgery to giving correct date of birth and day of the week (wake-up time) were recorded. There were no significant differences between the four groups in any of these observations, as reported previously to the society [1]. In particular, the spontaneous respiration with isoflurane group had the longest mean time to correct date of birth (8.11 (SD 2.4) min) while the ventilation/infusion group had the shortest mean time (7.20 (3.7) min). These observations were correlated within each anaesthetic group with the wake-up time using the Spearman rank correlation. Because of the multiple tests (four) within each anaesthetic group, a *P* value of less than 0.01 was considered significant.

Although there was a suggestion of correlation with age in one group and induction–incision time in another, these were not considered statistically significant (table XII). There was, however, a significant positive correlation in the spontaneous respiration–isoflurane group between duration of anaesthetic and wake-up time. There was also a significant negative correlation in the ventilation–propofol group between duration of anaesthetic and wake-up time.

Inspection of the raw data does not reveal any "rogue" values. All four groups had similar mean ages, weights, induction–incision times, duration of anaesthetic and wake-up times, with no significant differences between groups. The observed significant correlations may either be totally erroneous or imply a real relationship.

TABLE XII. *Spearman rank correlation with wake-up time in the four groups.* $^{**}P < 0.01$

	Spontaneous respiration		Ventilation	
	Isoflurane	Infusion	Isoflurane	Infusion
No. of patients	30	30	28	28
Age	0.24	0.04	0.65	0.58
Weight	0.42	0.35	0.59	0.56
Induction–incision	0.021	0.46	0.43	0.61
Duration	0.006**	0.40	0.52	0.002**

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A SURVEY OF POSTANAESTHETIC SEQUELAE FROM THE PATIENT'S VIEW: THE INCIDENCE OF THIRST AND MOUTH-DRYNESS

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Thirst, a symptom of non-pathological fluid deficiency, is normally satisfied by drinking. This process is disturbed by fasting before operation. After operation, the fluid deficit may worsen in spite of i.v. fluids and the availability of water. The objective of this study was to quantify the incidence of thirst and mouth-dryness in the postoperative period and to identify susceptible groups. The results could be used in audit and quality management.

Anaesthetists and patients were asked to identify factors that made patients uncomfortable in the first 24 h after surgery. These comments were collated and rewritten as questions for a patient-completed form, each to be answered "yes" or "no". The audit co-ordinator distributed and collected completed forms when visiting patients. Statistical analysis was undertaken using EPI Info 5 [1]. The chi-square test was used for nominal data and the Mann–Whitney or Kruskal–Wallis test for ordinal data. A probability less than 0.05 was considered significant and less than 0.01 highly significant.

Data from 3776 patients were studied. Thirst and mouth-dryness were reported by 62.4% and 61.7% of patients, respectively. More females (65.7%) reported thirst than males (58.2%). The mean age of patients reporting thirst was 49.2 yr compared with 53.1 yr for patients not reporting thirst ($P < 0.01$). Thirst and mouth-dryness were highly significantly associated with each other and with nausea, preoperative anxiety and general anaesthesia (*vs* regional anaesthesia). Thirst and mouth-dryness were more frequent in acute surgical, general surgical and gynaecological wards. In summary, patients most likely to be thirsty were females given general anaesthetics for acute surgical, general surgical or gynaecological procedures.

Although thirst and mouth-dryness are potential postoperative complaints, there has been no large study quantifying the problem. An incidence of over 60% cannot be ignored. Thirst and mouth-dryness are important because they are unpleasant and may also indicate significant fluid deficit. These patients may be less able to tolerate perioperative problems, for example haemorrhage, and more likely to develop postoperative complications. Modified preoperative fasting and perioperative fluids may be important in reducing these complaints.

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ONDANSETRON, DROPERIDOL AND SALINE FOR THE PREVENTION OF NAUSEA AND VOMITING AFTER MAJOR ORTHOPAEDIC SURGERY. A DOUBLE-BLIND CONTROLLED STUDY

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The incidence of postoperative nausea and vomiting (PONV) may be as great as 83% after major orthopaedic surgery [1]. In the only published comparative trial with other routinely used antiemetics, ondansetron, a selective $5HT_3$ antagonist, has been shown to be superior in preventing PONV after minor gynaecological procedures [2]. The aim of this study was to compare its efficacy against droperidol and saline in patients after major orthopaedic surgery.

One hundred ASA I and II patients undergoing hip and knee replacements and femoral resections were studied. They received a standardized combined extradural of 0.5% plain bupivacaine 10 ml and general anaesthesia with temazepam 20 mg as premedication, propofol 2.5 mg kg^{-1} as induction agent, 66% nitrous oxide and 2% enflurane in oxygen, breathing via a laryngeal mask. At the end of surgery they were randomized to receive either droperidol 1.25 mg, ondansetron 4 mg or 0.9% saline in a 25-ml bag. These were previously prepared by the Pharmacy Department and were given i.v. over 10 min. An extradural mixture containing 0.5% plain bupivacaine 10 ml, fentanyl 500 μg and saline 30 ml was infused. A nausea and vomiting chart was recorded by the nursing staff four-hourly for 24 h. Side effects, administration of rescue antiemetic (metoclopramide 10 mg i.m.) and volume of extradural mixture used were also recorded.

Age, weight, gender and duration of operation were similar between groups. Both ondansetron and droperidol were superior to saline in preventing PONV ($P < 0.01$, chi-square test) (table XIII), although no significant difference was seen between them. However, metoclopramide was demanded by 38%, 32% and 11% of saline, droperidol and ondansetron patients, respectively (droperidol *vs* ondansetron, $P < 0.05$, chi-square test). Side effects from ondansetron and droperidol were minimal. There was no difference in the volume of extradural mixture used between groups.

TABLE XIII. *Incidence of postoperative symptom-free, nausea and vomiting in ondansetron, droperidol and saline groups*

Group	*n*	No symptoms (%)	Nausea (%)	Vomiting (%)
Ondansetron	35	22 (63)	8 (23)	5 (14)
Droperidol	31	18 (58)	9 (29)	4 (13)
Saline	34	9 (26)	8 (24)	17 (50)

Although ondansetron and droperidol were equally effective in suppressing PONV, the reduced requirement for metoclopramide may suggest that ondansetron provides greater subjective benefit.

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DOES CHOICE OF DAY-CASE ANAESTHETIC AFFECT POSTOPERATIVE MORBIDITY?

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A previous presentation to the society has demonstrated a surprisingly high postoperative morbidity after various day-case procedures [1]. Another presentation of four anaesthetic techniques for day-case oral surgery failed to demonstrate any significant difference in speed of wake-up, judged by time to correct orientation and giving correct date of birth [2]. We now present the follow-up data to this study.

Patients aged between 18 and 45 yr, ASA I, presenting for day-case oral surgery on an afternoon list were anaesthetized with one of four anaesthetic techniques as described previously [2]. Patients were allocated randomly to spontaneous respiration with 1.5–2 % isoflurane, spontaneous respiration with propofol–alfentanil infusion 15/12/9 mg kg h^{-1}, IPPV with 0.5 % isoflurane and IPPV with propofol–alfentanil infusion 7.5/6/4.5 mg kg h^{-1}.

All patients were visited at home on the first and second days after operation, usually in the morning, by one of the investigators (S.O.S.) who was unaware of the anaesthetic technique used. A number of indices of wellbeing were established, following a semistructured interview. Overall activity was assessed and scored 0–3 (0 = still in bed, 1 = up but with extensive assistance, 2 = up without assistance, 3 = full return to normal activity/work). Appetite (0–3), operation site pain (0–3) and nausea and vomiting (yes/no) were also scored.

We present results on the first 20 patients to be followed-up in each group. Patients had been excluded if follow-up was not made on at least the first day after operation. There were no significant differences in mean age, weight, sex distribution or duration of anaesthetic between the groups or in any indices after operation (table XIV).

We were surprised that choice of anaesthetic had no effect on postoperative morbidity. Our methods of assessment might have been too crude, although a swift return to normal activity (score 3) must be an important objective of day-case anaesthesia. Also, the morbidity of the surgery could swamp the anaesthetic morbidity. Finally, patients (and others) perhaps expect to be "laid up" for several days after an anaesthetic. Results from this study combined with our previous presentation [2] must make us question our methods of assessment.

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ANALYSIS OF THE EEG USING CHAOTIC DYNAMICS

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It is not known with certainty if the EEG is dominated by noise or if it obeys the laws of chaotic behaviour and if so, if anaesthesia influences this EEG behaviour.

Several measures, taken from non-linear dynamic modelling, were used to quantify changes in raw EEG data in subjects at different end-tidal concentrations of isoflurane. Each EEG segment was recorded for 16 s, the sampling frequency was 8192 Hz with a filter roll-off of 2.78 kHz. Data were decimated by a factor of 8 and each data file contained 16384 data points. Measurements were made at zero then 0.2 %, 0.4 %, 0.2 % then zero end-tidal isoflurane. Two other data sets were also used, one of which was from the same subject as the above study, but recorded at a different time. These EEG were recorded just after an evoked response experiment and each data set was recorded for 2 s for end-tidal isoflurane of zero then 0.2 %, 0.4 %, 0.6 % and 0.8 % (returning in the same steps to zero). As a control on the functioning of the algorithms, three other data sets were analysed. These were: (1) chaotic data generated from the Lorenz system; (2) coloured $1/f^{a}$ noise; and (3) white Gaussian noise. Several new programs were used in this study, one of which was designed to differentiate noise from chaos.

The first phase showed that for all of the data studied, the test statistic from the program revealed that all of the EEG data analysed were chaotic whereas the two noise control data sets were not. The second phase was to try and quantify the chaos and to see if the quantification changed with anaesthetic concentration. To quantify the chaotic behaviour, the correlation dimension, embedding dimension and Lyapunov exponents were measured.

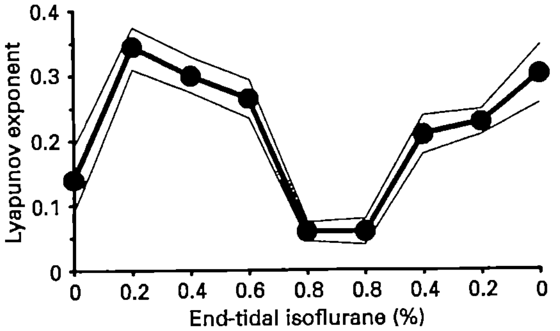

FIG. 7. Changes in the Lyapunov exponent in one subject with varying concentrations of end-tidal isoflurane.

TABLE XIV. *Mean (range) postoperative indices in the four groups.* n = *20 in each group*

	Spontaneous respiration		Ventilation	
	Isoflurane	Infusion	Isoflurane	Infusion
Activity				
Day 1	1.45 (0–3)	1.30 (0–2)	1.60 (0–3)	1.60 (0–3)
Day 2	2.10 (0–3)	1.93 (0–3)	2.21 (0–3)	1.95 (0–3)
Appetite				
Day 1	1.22 (0–2)	1.33 (0–2)	1.45 (0–2)	1.26 (0–2)
Day 2	1.60 (0–2)	1.59 (0–2)	1.89 (0–3)	1.60 (0–2)
Op. site				
Day 1	1.80 (0–3)	1.65 (0–3)	1.45 (0–3)	1.39 (0–3)
Day 2	1.60 (0–3)	1.50 (0–3)	1.25 (0–3)	1.35 (0–3)
Nausea/vomiting				
Day 1	6/20	3/20	3/20	3/20
Day 2	1/20	0/20	0/20	3/20

The plots of the correlation dimension *vs* embedding dimension did not show a well defined saturation as one would expect for a pure chaotic system. This lack of saturation is thought to be a result of the presence of noise in the EEG data. The correlation dimension and the Lyapunov exponents are quantities that measure the predictability of the data time series and hence are measures of the information processing capacity of the brain. In these experiments we found an increase then a decrease in these quantities for the subjects with increasing isoflurane concentration.

Figure 7 shows these changes in the Lyapunov exponent. For the recovery stages with decreasing anaesthetic concentration, we found a systematic increase in both correlation dimension and Lyapunov exponent.

The EEG shows chaotic behaviour and the quantitative measures of chaos change with anaesthetic concentration. As the level of anaesthetic agent is increased, the variables increase then decrease. However, as the concentration of anaesthetic agent is decreased from a stage where subjects were unresponsive, a systematic increasing trend has been obtained.

POSTER PRESENTATIONS

INFLUENCE OF PRELOAD ON POST-SYSTOLIC SHORTENING

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Regional wall motion abnormalities detected by echocardiography have been used as markers of ischaemia. In coronary artery bypass surgery, absence of such abnormalities after bypass has been associated with a better outcome [1]. Post-systolic shortening (PSS) is an abnormality easily demonstrated in open-chested animal models. It is defined as the shortening of cardiac muscle occurring after the end of ejection.

Eleven mongrel dogs were acutely instrumented for measurement of pressure (left ventricle and aorta), flows (aorta and left anterior descending artery (LAD)) and dimensions in the near apical (LAD territory) subendocardium. Anaesthesia was maintained with 70 % nitrous oxide and 0.8 % halothane in oxygen and controlled ventilation to normocapnia. Myocardial ischaemia in the LAD segment was obtained by tightening a micrometer controlled snare. Slow stepwise loading and unloading was achieved by infusion and withdrawal of four 50-ml aliquots of blood over 30 min. PSS was calculated as end-systolic length minus minimum length during diastole and expressed as a percent of end-systolic length. Data were analysed using ANOVA and paired *t* tests with Bonferroni's correction.

Increasing the preload over the range of 4–24 mm Hg caused significant reductions in PSS (fig. 8).

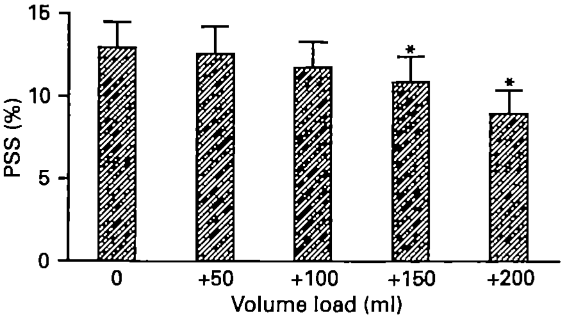

FIG. 8. Relationship between volume load and post-systolic shortening (PSS). Values are mean, SEM. $^*P < 0.05$.

This study demonstrates that the amount of PSS is sensitive to volume status, which therefore has to be taken into account in interpreting regional wall motion abnormalities. As PSS is a marker of ischaemia [2], this study suggests that an increase in preload may reduce rather than increase ischaemia.

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PATTERNS OF CHANGE OF INSULIN-LIKE GROWTH FACTORS AND THEIR BINDING PROTEINS AFTER ABDOMINAL SURGERY

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The insulin-like growth factors (IGF-I and IGF-II) are peptides with both mitogenic and insulin-like properties. They circulate in the plasma [1], bound to specific binding proteins (IGFBP-1,2,3,4,5 and 6), from which it is postulated that some are released by proteases. IGF are thought to be important regulators of anabolism and glucose metabolism. Total plasma IGF-I decreases after surgery [2] and therapeutic intervention has been suggested to reverse this. This study was designed to establish the effects of major surgery (laparotomy for bowel surgery) on IGF-I and IGF-II and IGFBP-1, 2 and 3.

Twelve adults (three male), aged 30–70 yr, ASA classes I–III, gave informed consent to the study. Exclusion criteria included endocrine abnormalities and treatment, including steroid therapy. All subjects received standardized premedication with papaveretum and hyoscine, and general anaesthesia was induced with thiopentone, maintained with nitrous oxide and enflurane in oxygen and mechanical ventilation was facilitated using atracurium. Blood was sampled before premedication, at induction of anaesthesia, at the end of surgery, 2 and 6 h after surgery, and then daily fasted morning samples were obtained on days 1–4, 7 (and if still in hospital 10, 14) and at the 6-week outpatient visit. Plasma glucose, insulin and C-peptide concentrations were assayed. Body weight, skin-fold thickness and urinary nitrogen excretion were also measured.

Mean total plasma IGF-I decreased from the value before operation by 13 % during surgery and by 39 % by day 4. Patients still in hospital demonstrated recovery to baseline values between days 10 and 20, and the mean value increased to 13 % above baseline by 6 weeks. IGF-II followed a similar biphasic decrease, again recovering from day 4. The IGFBP underwent dissimilar patterns of change. Only IGFBP-3 (the main plasma IGF carrier) followed the same downward trend as the IGF, recovering gradually from day 3. In contrast, mean plasma IGFBP-I was transiently, markedly increased during surgery (183 % greater than the value before operation by the end of surgery). Mean plasma IGFBP-2 decreased slightly during surgery and then increased to 35.5 % greater than the baseline value by 6 h after surgery. This remained increased until day 14 and then decreased to 18.1 % less than baseline by 6 weeks.

Glucose, insulin and C-peptide concentrations behaved predictably, showing an increase during surgery and subsequent return towards baseline by day 2. The nutritional status indices also behaved as expected. The differing IGFBP response patterns have not been described previously. Radically altered perioperative IGFBP regulation is suggested by the surprising failure to maintain the usual inverse relation between IGFBP-1 and insulin. That IGFBP-2 increased as IGF-II decreased is also a new finding. These results have important implications for future therapeutic trials of growth hormone or IGF administration.

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POSTURE AND INTERNAL JUGULAR VEIN SIZE STUDIED WITH THE "SITERITE" ULTRASOUND DEVICE

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Catheterization of the internal jugular vein is an invasive procedure commonly carried out by anaesthetists. Successful location of the vein at the first attempt reduces the risk of morbidity and mortality, leading to the introduction of devices [1] such as the "Siterite" portable ultrasound. We have used one of these devices to investigate the effects of head-down tilt and head turning on internal jugular vein size and position, a technique in accepted use [2].

Nineteen volunteers aged between 22 and 50 yr took part in this study. Each lay supine on an intensive care bed with one pillow and cricoid cartilage was located and marked. Using the Siterite (Dymax, U.S.A.) probe, the right internal jugular vein was located at this level, using the carotid pulse as a marker. The probe was placed perpendicular to the skin and the image of the vein centralized on the screen of the device, with the volunteer's head in a neutral position. A photograph was then taken of the screen using a camera with a long focal length lens (135 mm) set on a tripod at a fixed distance from it, with an exposure of 1 s. This process was repeated for each volunteer with the bed tilted head down by 10° (two "clicks" on the ratchet mechanism) and 20° (four clicks). A further picture was taken at 10° with the head turned by 45° away from the sagittal plane.

Each photograph was then traced using back illumination onto 1-mm squared graph paper and measurements taken of the vein for maximum anterior–posterior diameter, cross-sectional area and depth from skin to anterior border (table XV).

TABLE XV. *Mean* (SD) *measurements of the vein* (*mm*) *for maximum anterior–posterior* (*A–P*) *diameter, cross-sectional area and depth from skin to anterior border. All increases in diameter and area are significant* ($P < 0.01$, *paired* t *tests*)

Position	A–P diameter	Area	Depth
Flat	6.5 (2.4)	32.8 (19.2)	12 (2.7)
10° tilt	8.6 (2.5)	51.2 (27.5)	11.4 (2.4)
10° + turn	9.8 (2.4)	50.7 (29.5)	13.8 (3.2)
20° tilt	10.3 (2.4)	70.4 (40.3)	10.9 (2.3)

The Siterite is a useful tool for the investigation of superficial blood vessels and steep head-down tilt doubles the size of the internal jugular vein in normal volunteers.

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British Journal of Anaesthesia 1993; **71**: 772–775

CORRESPONDENCE

THE LARYNGEAL MASK FOR INTRAOCULAR SURGERY

Sir,—Ripart, Cohendy and Eledjam [1], in commenting upon the article by Lamb, James and Janicki [2], described two untoward incidents associated with the use of the laryngeal mask airway (LMA) for controlled ventilation during intraocular surgery. As a result, they have abandoned the technique. They have done so without relating the incidents to their total experience of the LMA and without quantifying the complications associated with tracheal intubation.

Our own clinical experience of LMA use with controlled ventilation in intraocular surgery during the past 2 years supports the original contentions of Lamb, James and Janicki [2]. Our audit data show that, in 593 uses, there were six difficult placements (five were eventually successful, while in the sixth the trachea was subsequently intubated); one LMA became displaced during the procedure but was repositioned quickly and successfully and there was one case of gastric distension because of malplacement which was corrected before surgery commenced. Only the last two incidents presented a significant clinical problem (0.3 % of the total use). Neither resulted in morbidity. Over the same period this compared with a 1.6 % incidence of serious problems with the use of tracheal tubes (three of 187 uses): one case of laryngeal spasm, one difficult intubation and one episode of pulmonary oedema at extubation.

For all our surgical specialties, 135 incidents were reported in 3974 tracheal intubations (3.4 %): 120 difficult placements and 15 episodes of laryngeal spasm. There were 52 incidents in 5655 LMA uses (0.9 %): 45 difficult placements and seven episodes of laryngeal spasm (chi-square = 73.93; $P < 0.001$).

With sufficient experience, use of the LMA can provide improved operating conditions for intraocular surgery and a smooth recovery with a small incidence of serious problems. Contrary to the anecdotal comments of Ripart, Cohendy and Eledjam, our data support use of the LMA for controlled ventilation in intraocular surgery.

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1. Ripart J, Cohendy R, Eledjam J-J. The laryngeal mask and intraocular surgery. *British Journal of Anaesthesia* 1993; **70**: 704.
2. Lamb K, James MFM, Janicki PK. The Laryngeal mask airway for intraocular surgery: effect on intraocular pressure and stress responses. *British Journal of Anaesthesia* 1992; **69**: 143–147.

Sir,—Ripart, Cohendy and Eledjam [1] described two cases of LMA displacement associated with use in paralysed patients undergoing artificial ventilation for intraocular surgical procedures.

These cases serve to illustrate the dangers of incomplete understanding of how to use this deceptively simple instrument. Because of its anatomical position, the LMA provides a leak-free seal permitting positive pressure ventilation, provided that:

(1) The laryngeal muscles, including the vocal cords, remain sufficiently relaxed throughout the procedure;

(2) total resistance to inspiration is not permitted to increase to a point exceeding the leak pressure;

(3) it is inserted, inflated and secured correctly in the first instance.

Having observed anaesthetists of all grades in 16 countries learning to use the LMA, I am confident that the commonest cause of the sequence of events described by Ripart, Cohendy and Eledjam is failure to maintain a level of anaesthesia or neuromuscular block appropriate for the procedure.

The correctly placed and secured LMA does not migrate spontaneously from its position during surgery. However it is sometimes forced upwards out of the hypopharynx if cricopharyngeal muscle tone is permitted to increase. Much more frequently, leaks are heard initially because the vocal cords begin to close, associated with an inadequate degree of neuromuscular block. One of two errors is then made commonly:

(1) Inflation of excessive air into the cuff, which in turn causes the mask to be forced upwards out of the hypopharynx, exacerbating the leak.

(2) Attempting to readjust the mask in the belief that it is misplaced, resulting in stimulation to the larynx and thus further increasing the tendency for this to close, so again exacerbating the original leak. This misunderstanding is perhaps particularly likely when the device is hidden from view under drapes.

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1. Ripart J, Cohendy R, Eledjam J-J. The laryngeal mask and intraocular surgery. *British Journal of Anaesthesia* 1993; **70**: 704.

TRACHEAL TUBE CUFF INFLATION AS AN AID TO BLIND NASOTRACHEAL INTUBATION IN A PATIENT WITH CERVICAL SPINE INJURY

Sir,—I read with interest the article of Van Elstraete and colleagues on tracheal tube cuff inflation as an aid to blind nasotracheal intubation [1]. Inflation of the tracheal cuff in the oropharynx is assumed to centre the tip of the tube and to direct it anteriorly towards the larynx. The authors showed a high success rate when the technique was used in anaesthetized and paralysed patients with a normal airway, whose head and neck can be manipulated safely to place the head in the "sniffing" position before tracheal intubation. However, it remains to be established if the technique improves the success rate of blind nasotracheal intubation in cases of difficult intubation

I have recently tried the technique for awake blind nasotracheal intubation in a 26-yr-old male patient who suffered cervical spine fracture. The spinal cord was intact and the patient was brought to the operating room in traction for cervical spine fixation. Traction or manual in-line stabilization, although reducing cervical spine movement, places the oral, pharyngeal and laryngeal axes out of alignment and makes orotracheal intubation more difficult, therefore, it was planned to proceed with awake blind nasotracheal intubation before positioning the patient and induction of general anaesthesia. After topical anaesthesia was applied, a size 8.0 mm polyvinylchloride cuffed tracheal tube was introduced via the right nostril into the oropharynx. While the cuff of the tube was deflated, blind tracheal intubation was attempted. However, three attempts failed to achieve intubation. The procedure was abandoned, and it was decided to try tracheal tube cuff inflation as an aid to blind nasotracheal intubation. The cuff of the tube was inflated in the oropharynx with 20 ml of air, and the tube was advanced gently while the patient was breathing spontaneously. Slight resistance was felt, while free air movement continued through the tube, denoting entry of the tip of the tube into the glottis and contact of its inflated cuff with the vocal cords. At that time, the cuff was deflated, the tracheal tube was advanced into the trachea and the cuff was reinflated.

This experience demonstrated that the cuff inflation technique can facilitate awake blind nasotracheal intubation in cases of cervical spine injury which may not allow or may even contraindicate manipulation of the head and neck to achieve the "sniffing" position.

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Sir,—We agree that this technique may be of use in such patients. Although patients in our study were anaesthetized and paralysed and the cervical spine was in the "sniffing" position, we are encouraged by the case report regarding an awake patient. We have noted that the technique appears equally successful when the cervical spine is immobilized in a neutral position. Awake tracheal intubation in cases of cervical spine injury allows neurological assessment during and after the procedure and it is claimed, although without supporting data, that preservation of muscle tone may provide some protection. Further studies are required in this patient population, using the technique of cuff inflation to define success rates, amount of cervical spine movement and effects on patient outcome. Studies comparing this technique with others such as awake fibreoptic intubation would also be of interest.

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USE OF ALFENTANIL AND PROPOFOL FOR DIFFICULT TRACHEAL INTUBATION

Sir,—In the letter from Coghlan, McDonald and Csepregi [1], it was suggested that the use of alfentanil and propofol for tracheal intubation [2] may be useful for management of the difficult airway. We have recently had the opportunity to use this technique successfully for such a case.

A 25-yr-old female presented 5 days after extraction of her wisdom teeth under local anaesthetic. She had developed a large right parapharangeal abscess which severely restricted mouth opening to a maximum of 1 cm between upper and lower incisors.

We elected to induce anaesthesia with halothane in oxygen and perform nasotracheal intubation using a fibreoptic laryngoscope. Unfortunately, because of the large parapharangeal swelling and subsequent distorted anatomy, we were unsuccessful. Attempts were made at blind nasal intubation, but these were also unsuccessful because of the nasotracheal tube being deflected by the parapharangeal swelling. Laryngoscopy was impossible under deep inhalation anaesthesia, as the mouth would still not open more than 1 cm.

We were able to maintain an airway while the patient was breathing spontaneously, but had difficulty ventilating the lungs using a face mask and hence were reluctant to use a neuromuscular blocker for fear of losing control of the airway. We therefore decided to use the combination of alfentanil and propofol, with the ability to antagonize the effects of the alfentanil rapidly using naloxone, if this should be necessary. We gave alfentanil 25 $\mu g\,kg^{-1}$ followed by propofol 1 $mg\,kg^{-1}$. This enabled us to open the mouth 2 cm and perform laryngoscopy. We were able to visualize the tip of the epiglottis and intubate the trachea with the aid of a bougie

We feel that this is a useful alternative technique, when used by experienced operators, for managing a patient with a difficult airway.

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THE $P < 0.05$ CRITERION IS NOT INVIOLABLE

Sir,—It is interesting to read that single stimuli every 10 s and train-of-four stimulation every 10 s yield different estimations of the potency of mivacurium. Maddineni and colleagues [1] reported that the leading twitch (T1) of the train-of-four exhibited a deeper block than the single twitch (T). The authors suggested, plausibly, that the more intense train-of-four stimulation itself and the secondary improvement in blood flow to the muscle hasten the onset and deepen block of T1. Another factor likely to contribute to the deeper block of T1 is that a train-of-four every 10 s allows less rest between stimulations (8.5 s *vs* 10 s).

I wish also to comment on the authors' conclusion that T differs from T1 *significantly* for ED$_{50}$ (43 *vs* 35 $\mu g\,kg^{-1}$ ($P = 0.03$)), *insignificantly* for ED$_{95}$ (83 *vs* 66 $\mu g\,kg^{-1}$ ($P = 0.051$)), and *insignificantly* for slopes of the dose–response curves. It is not logical that there should be a difference in only one of the two points of the regression lines without a difference in the slope.

Many authors and reviewers inflexibly adopt the *customary* "$P < 0.05$" criterion. Some even object to the notation of $P = 0.01$, $P = 0.1$, etc. and insist that either "$P < 0.05$" or "ns", and nothing else, be printed. Some further equate "statistically not significant" with "not different".

Others—a minority to which I belong—are more wary of the danger of type II error associated with small sample size in a highly variable population [2]. They point out that the $P < 0.05$ criterion is artificial. Borderline P values should be revealed [1, 2]. "Statistically not significant" is not "not different". If the means are not different, t tests rarely need to be done.

Taking the example of Maddineni and colleagues' study, great individual variability in data existed, as expected. Instead of describing $P = 0.051$ as insignificant but $P = 0.03$ significant, I would call both comparisons significant to $P < 0.075$. This leaves a 92.5% chance that the two differences in ED values are both significant, and allows the logical conclusion that the two regression lines are parallel. In other words, I would reject the $P < 0.05$ criterion. The authors' overall conclusion was in favour of the difference.

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Sir,—I agree entirely with the sentiments expressed by Dr Lee. He has obviously noted that the difference between the ED$_{95}$ values was also very close to being significant ($P = 0.051$). This was the aim of our giving the actual P value rather than simply saying that the difference was insignificant.

We are glad to see that Dr Lee agrees with the conclusions we had reached and I hope others will reach similar conclusions. I also agree with him that to describe a difference as significant at $P < 0.05$ is only arbitrary, although conventional.

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SPINAL NEEDLE: AN UNUSUAL COMPLICATION

Sir,—We read with interest the report on "Concorde nose" in Whitacre spinal needles in which McLeod, Carson and Bannister illustrated the point that, if a Whitacre needle strikes bone, the needle should be removed and discarded [1]. The side hole in a pencil-point needle renders it weak and thus makes it more prone to bending. We recently encountered bizarre bending of the stilette of a bevelled re-usable spinal needle, presumably after striking bone.

A 37-yr-old ASA I female was to undergo vaginal hysterectomy under spinal anaesthesia. A 23-gauge bevel-tipped spinal needle was introduced slowly at the L3–4 interspace with the patient in the left lateral position. Resistance was felt at a depth of about 4 cm and, on the presumption that the needle had entered the ligament flavum, a slight increase in force was made. After some resistance, the needle moved in with a jerk. Believing that the needle had by then entered the subarachnoid space, the resident attempted to remove the stilette, but could not. On a second attempt, the hub sheared off at the junction with the shaft, which stayed inside the needle. An attempt was then made to withdraw the needle and the stilette together, but although the needle was removed, the stilette (without hub) remained *in situ*. By increasing the flexion of the spine, it was possible eventually to remove the stilette, using some force. After removal, the tip was found to be

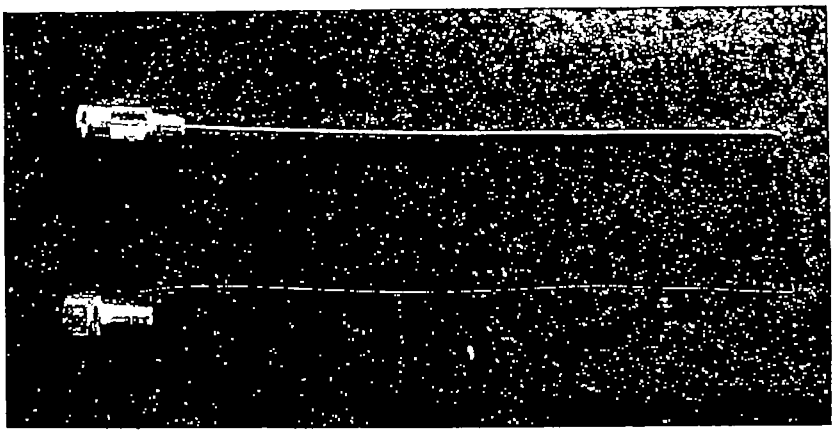

FIG. 1. The needle, detached stilette hub and bent stilette.

bent at about 90° (fig. 1). Subsequent queries revealed that, before performing the block, the resident had noted the stilette projecting beyond the needle bevel by about 2 mm, but did not anticipate any trouble.

We suspect that, when the initial resistance to advancement of the needle was felt, it had come into contact with bone. When the needle was pushed further, the tip of the stilette (beyond the bevel) bent over at the heel of the bevel and this prevented its removal.

Interchange of the stilette of one needle with another may result in the stilette projecting beyond the needle. This is likely to occur at the time of packing of the "spinal set" before sending it to the Central Supply Department for sterilization. We suggest that, if the stilette is noted to project beyond the bevel of a needle, the needle should be discarded.

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1. McLeod GA, Carson D, Bannister J. "Concorde nose" in Whitacre spinal needles. *British Journal of Anaesthesia* 1993; 70: 593.

ANALGESIA INDUCED BY METOCLOPRAMIDE

Sir,—We found the recent paper by Lisander [1] most interesting. We agree with the author that the mechanism of metoclopramide analgesia is yet to be elucidated. It has been suggested that metoclopramide *per se* exhibits potent analgesic activity in rats and that metoclopramide-induced analgesia is opioid-mediated as it is antagonized by naloxone [2]. However, metoclopramide is also a dopaminergic antagonist which has been shown to increase prolactin concentrations in animal models and in humans [3], and it has been suggested that metoclopramide-induced analgesia might be prolactin-mediated. Indeed, prolactin has been shown to produce analgesia in rats; the mechanism of prolactin-induced analgesia is probably both opioid and dopaminergic-mediated [4].

We have investigated the binding of both metoclopramide and prolactin to opioid receptor sites in the human SH-SY5Y neuroblastoma cell line [5]. The binding studies were performed using whole SH-SY5Y human neuroblastoma cells incubated at 37 °C for 1 h in 1-ml volumes of Krebs–HEPES buffer pH 7.4. Binding affinities were calculated by assessing the displacement of a fixed concentration (0.2–0.4 nmol litre^{-1}) of the non-selective opioid antagonist, [^{3}H]diprenorphine, by increasing concentrations of morphine, metoclopramide and prolactin.

Our data (table I) suggest that analgesia induced by metoclopramide or prolactin is not directly or indirectly dependent on opioid receptor occupancy by these agents.

In agreement with Lisander, we can only conclude that the mechanism by which metoclopramide exerts its analgesic action remains unknown, and warrants further study.

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SORE THROAT AFTER SUXAMETHONIUM

Sir,—I am pleased to be able to supply evidence in support of Dr Deacock's suggestion that sore throat is indeed part of the clinical picture of suxamethonium pains [1]. We studied the muscle pains

TABLE I. *Effects of morphine, metoclopramide and prolactin on [^{3}H]diprenorphine binding to whole SH-SY5Y human neuroblastoma cells (mean (SE or range))*

	Binding affinity	Typical plasma concentrations
Morphine ($n = 5$)	99 (11) nmol litre^{-1}	12–273 nmol litre^{-1} [6]
Metoclopramide ($n = 5$)	> 30 μmol litre^{-1}	100–300 nmol litre^{-1} [7]
Prolactin ($n = 3$)	> 50 ng ml^{-1}	5–8 ng ml^{-1} [8]

and sore throat that developed after general anaesthesia for minor gynaecological surgery, of less than 10 min duration, in almost 900 patients who had given informed consent [2]. Patients were allocated randomly to two groups. One group received suxamethonium 1 mg kg^{-1} after induction of anaesthesia and underwent manual ventilation of the lungs with nitrous oxide via face mask. The other group breathed nitrous oxide spontaneously and anaesthesia was maintained with increments of the chosen induction agent. Tracheal tubes were not used and Guedel airways inserted only in a small number of patients (4%) with difficult airways; these were excluded from further analysis.

Whilst the overall incidence of suxamethonium pains in 407 patients was found to be 52%, the incidence of sore throat in this group was 19%, compared with 3.2% in the non-paralysed group ($P > 0.001$). In 81% of the patients with sore throat following suxamethonium, typical muscle pains also developed, usually involving neck pain or stiffness as a major component (85%). It is difficult to attribute the sore throat to any other factor, unless the brief period of intermittent positive pressure ventilation exerted some effect on the pharynx or larynx.

Thus it does appear as if sore throat is another manifestation of suxamethonium pains, presumably because of action of the agent on the muscle spindles of the laryngeal or pharyngeal muscles, although this has not been demonstrated [2]. As Deacock pointed out [1], suxamethonium must be taken into account when postoperative sore throat is assessed and this depolarizing agent has been used.

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POSTDURAL PUNCTURE HEADACHE AND EXTRADURAL BLOOD PATCH

Sir,—We read with interest the editorial on the use of extradural blood patches in dural puncture headache [1]. We have recently treated a 47-yr-old lady who presented to the neurologists with a 6-week history of headache secondary to a spontaneous dural leak of CSF.

This cause of headache is very rare, with only a small number of case reports in neurological journals [2]. The signs and symptoms are identical to those found in patients with dural punctures who are seen by anaesthetists.

Investigation of this lady by the neurologists demonstrated a collapsed ventricular system on CAT scan, with decreased CSF pressure and caudal extension of dye on the myelogram. It was thought that the defect in the dura was probably in the lumbar region, so we performed a lumbar extradural blood patch. This produced some relief within 15 min, and by the next day she was able to go home.

Previous case reports have described conservative treatment [3], with blood patch used as a last resort [4]. This case adds further evidence to the signs and symptoms of dural puncture headache being secondary to decreased CSF pressure.

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British Journal of Anaesthesia 1993; 71: 776–777

BOOK REVIEWS

Les Brûlures. By C. Echinard and J. Latarjet. Published (1993) by Masson, Paris. Pp. 336; indexed; illustrated. Price FFr 240.

This concise book consists of four parts and is co-written by a surgeon and an anaesthetist, both of whom have considerable experience in the management of burns caused mainly by thermal injury.

The first part is devoted to the epidemiology, prevention and organization of the care of burns in France. Indeed, the first European burns unit was founded in Lyon in 1952. The epidemiology of burns is virtually unknown, despite a recent epidemiological study undertaken world-wide jointly by the World Health Organisation and the International Society for Burn Injuries. However, this chapter contains information about the European results of this study and compares the French approach to burn injuries with that of the rest of the world.

The second part deals with the physiopathology of burn injuries, with a great emphasis on the physiological, metabolic and immunological aspects of thermal injury and also gives a good descriptive account of the healing process. This chapter is concise and well written. It summarizes the modern concepts of burn physiopathology necessary for correct management of burn injuries.

The third chapter is a good guide to the therapy of burn injuries. It describes the immediate and late management of burns, including fluid management, and also gives an extensive account of the reconstructive treatment of burns by skin grafts. The chapter on the management of pain in the burned patient is clear and concise, but I was most interested by the chapter dedicated to the psychology and management of psychiatric problems of the burned.

The last part concerns the rehabilitation of burn patients and the prevention and treatment of hypertrophic scars and other sequelae of burn injuries. There is also a description of the long-term problems faced by the burn patient, namely the psychological and social problems.

The book also has an appendix which contains simple algorithms on the diagnosis, assessment and management of the burned patient.

Overall, this book is well-written, concise and clear. It should appeal to everyone dedicated to the treatment of burn injuries. The only disadvantage of this book is that it is written in French and thus of real value only to those fluent in that language.

B. Appadu

Surgical Intensive Care. Edited by P. S. Barie and G. T. Shires. Published by Little, Brown and Co., Boston, London, Toronto. Pp. 1364; indexed; illustrated. Price £167.50.

Before purchasing a book of this size, it is wise to go through a check list, such as the following: For whom is it intended? Who are the authors? Does the table of contents match the purchaser's requirements? How large is the index? How up to date and comprehensive are the chapter references?

When I addressed the first two questions the answers were that it was intended primarily for surgeons working in Intensive Care Units; all but 16 of the 91 authors are surgeons and only one of the others was identifiable as an anaesthetist.

In their introduction, the editors recognize the potential shortcomings of a volume of this size, such as inconsistency and repetition. It was their hope that the emphasis on basic principles which is applied throughout would allow future developments in pathophysiology and therapy to be assimilated. They state that the book is not intended to be a "cook-book" of intensive therapy but, even in a volume of this size, they have had to be very selective. However, they have succeeded in including some of the most important and most pressing problems within it. In addition to the obvious ones, which include sepsis, oxygen transport, cardiocirculatory, renal and respiratory failure and their treatment, there is a particularly good review of the need for available methods of severity scoring, which must be one of the most important un-answered questions of intensive therapy.

There is also a very comprehensive section which reviews many of the problems which accompany head injury. This section includes the psychological consequences of head injury and its treatment, the care of the unconscious patient and a discussion of brain death and the persistent vegetative state.

These and other topics are presented in adequate detail and in what, to the reviewer, appears to be a well balanced way. It would be neither realistic nor honest to profess to have read each section in equal depth, but certain subjects stand out, because of their relevance and presentation. There is a particularly good description of the factors which are currently believed to be responsible for the initiation and perpetuation of the sepsis syndrome, while the review of in-hospital cardiopulmonary resuscitation is refreshingly open in its approach.

Although most of this book is written by surgeons, nearly all of it is relevant and informative for anyone working in the field of intensive therapy. There is some superfluous surgical detail of procedures which would be performed only by the appropriate surgical specialist in this country. As might be imagined, there is little detailed description of the pharmacology of sedative, analgesic or muscle relaxant drugs, which are considered only briefly in the chapter on respiratory failure, but the sections which deal with inotropes, blood volume expanders (including blood transfusion) and the antibiotic treatment of sepsis are very good, as also is that concerned with the treatment of cardiac failure.

The index is 80 pages long and easy to use.

Where appropriate, each chapter begins with a short historical review, if that is the correct term for such a new subject, and ends with a comprehensive selection of references.

The lay-out of the book makes it a pleasure to handle. There are many clear tables and line drawings and the few photographs and radiographs which are reproduced are appropriate and easy to understand.

From its list of authors (and price) this book is clearly orientated towards the North American market, but it would be a great asset for any individual or departmental library. There are virtually no British or European contributors and the vast majority of references are to American journals. If that is a criticism, it is a mild one. Overall, this book has been a pleasure to review and is the best of its kind that I have seen.

J. C. Stoddart

Critical Care Management: Sedation and Analgesia. Edited by G. R. Park and F. Gempeles. Published by Harcourt Brace Jovanovich, Sidcup. Pp. 386; indexed; illustrated. Price £30.

This book aims to provide an overall review of the current practice of sedation and analgesia within the Intensive Care Unit. As it notes, it is difficult not to give a personal overview of how these activities are provided within one Intensive Care Unit. The book is separated usefully into sections on the needs and hazards of sedation and analgesia, with separate chapters on the pharmacology and pharmacokinetics of different classes of drugs.

Whilst the book is not a substitute for a pharmacology textbook, it does give a good account of how drugs should be expected to work within the Intensive Care setting. It concentrates on adult critical care management with, unfortunately, only a small amount of information on paediatric aspects. The choice of drug used, and the degree of sedation and analgesia, is the prerogative of the clinician responsible for the patient. The last chapter on case studies should be seen as anecdotal.

Overall, the book is a useful textbook, with a large number of references to which the reader can refer for more detailed aspects of the subject.

M. R. Ferguson

Controversies in Obstetric Anaesthesia, 2nd Edn. Edited by B. Morgan. Published (1992) by Edward Arnold, Sevenoaks. Pp. 139; indexed. Price £19.95.

This short book is based on the popular one-day Controversies Meetings organized over the past few years by the editor, Dr Barbara Morgan.

The book is compiled from the written texts of a series of debates on controversial issues in obstetric anaesthesia, each subject having a proposer and an opposer. The subjects range from preloading and ephedrine for regional techniques to the use of opioids in extradural practice. There are eight controversies, and an additional section updating information on previously debated controversial topics. Most contributions are from well known obstetric anaesthetists; others are not as well known. Most contributions have been researched well and contain a reference list at the end. Others have not been so well researched—one of the contributions, for example, stating that spinal anaesthesia for obstetrics has not found general acceptance in the U.K.!

I would single out as the outstanding topics in this edition, the use of regional techniques in the presence of fetal distress and the use of opioids in obstetric anaesthesia. The Controversies Meetings are held in front of a generally well informed group of obstetric anaesthetists and I agree with the editor that it is unfortunate that it was not possible to include some of the more incisive questions from the floor, together with an indication of the opinion of the audience on the various issues. Nevertheless, the book should be read by all obstetric anaesthetists, as it is important for all practitioners to keep up to date, especially with contentious issues.

R. J. S. Birks

Oxford Textbook of Palliative Medicine. Edited by D. Doyle, G. W. C. Hanks and N. Macdonald. Published by Oxford University Press, Corby. Pp. 845; indexed; illustrated. Price £95.00.

Palliative medicine physicians are justifiably proud of the progress that this specialty has made in recent years and the undoubted benefits that it has brought to many patients and their families. Books for reference in palliative care have previously been published and, while often excellent and extremely useful, most are small problem-solving books for symptom control.

The editors of this book have produced a comprehensive textbook, aimed specifically at doctors, which includes detailed information on all aspects of palliative medicine in one volume. The book is multi-authored, many being renowned experts in their particular field. The scope of the book is encyclopaedic, covering, in depth, not only the medical management of a wide range of conditions and symptoms, but also many relevant associated topics written by authors in the appropriate fields.

Section 2, entitled "The challenge of palliative medicine" sets the scene well. The chapters on the interdisciplinary team and communication are exceptional and contain information of immense practical value for use generally.

The majority of the book is devoted to symptom management. The arrangement of this section is good. Most of the chapters are of an extremely high standard and well written. I found those which deal with subjects outside my own specialty extremely informative and I learned new facts that will be useful in my everyday clinical practice. Those chapters dealing with my specialty (pain management) are comprehensive and consider both assessment and available treatment modalities.

Subsequent chapters in the book emphasize the contribution that other disciplines have in the management of the patient needing palliative care. Doctors involved in the organization of a hospice or palliative care unit and building a multidisciplinary team will benefit from these sections. The terminal phase of life frightens not only the patient and their family, but also many doctors. The chapter on this aspect discusses planning for this period and also gives excellent practical advice for use when this situation arises. The section on paediatric palliative care provides an all round insight into this distressing and difficult area. The chapters on psychological adaptation of the dying child and their family and special issues in bereavement are especially valuable and provide useful guidelines for working with the dying child and also helping children to cope with grief. Emotional problems in palliative medicine affect the patient and the family. The professional care-giver can also experience significant stress in response to dealing with dying patients. Specific strategies to recognize these problems and previously identified coping mechanisms are reviewed fully.

Many patients with acquired immune deficiency syndrome (AIDS) have chosen to have their medical care in units devoted specifically to this illness. However, it is inevitable that, as this disease becomes widespread, more patients will be cared for outside this setting. The chapter on palliative care aspects of AIDS is therefore valuable in educating and relating practical experience in a condition to which many of us have had little exposure.

This book fulfils its aim of being a comprehensive textbook of palliative medicine. The success in this aspect has, however, resulted in a book of some considerable size and weight, and it is uncomfortable to read other than at a desk in a formal manner. It is undoubtedly a first-class book, well-balanced and extensively referenced. There is a strong interdisciplinary perspective and this book will be a valuable source of knowledge and practical advice, not only to palliative medicine physicians, but also to doctors in other specialties and to other practitioners involved in the field of palliative care.

B. J. Collett

Collection d'Anesthésiologie et de Réanimation, volume 34: Anesthésie–Réanimation du sujet âgé. Edited by F. Servin. Published (1993) by Masson, Paris. Pp. 208; indexed; illustrated. Price FFr 270.

With the increasing number of elderly patients undergoing surgery, the anaesthetist is faced by many problems linked to the various chronic diseases that usually beset this population. This multi-authored monograph of the *Collection d'Anesthésiologie et de Réanimation* gives an overview of anaesthesia for the elderly.

The book consists of four parts: the first consists of four chapters dealing with the physiology of the aged and the pharmacology of anaesthetic drugs in the elderly. The second and third part deal mainly with the general aspects of anaesthesia and anaesthesia for specific procedures (e.g. prostatic surgery, ophthalmic surgery). The final part discusses the intensive care management of the elderly.

As may be expected for a multi-authored book, there is a wide variation in the quality of the chapters. Topics such as the choice between regional and general anaesthesia for the elderly and the role of ambulatory anaesthesia in the elderly are concise, clear and well referenced. I would have preferred to have a more detailed chapter on the recovery from anaesthesia with a particular interest on the recovery of the psychomotor function in the elderly.

Overall, this book is interesting and would be of value to all French-speaking anaesthetists caring for an elderly population.

B. Appadu

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

NEUROPATHIC PAIN: A CONDITION WHICH IS NOT ALWAYS WELL APPRECIATED

Neuropathic pain is caused by destruction of function in peripheral nerves, pain receptors (nociceptors) or the central pain pathway. The spectrum of neuropathic pain ranges from the neuropathies, post-herpetic neuralgia, some chronic scar pains, a proportion of the painful states following stroke, to phantom limb pain. As a consequence of the underlying degenerative changes in the pain pathway, conventional analgesic medication (non-steroidal anti-inflammatory drugs, paracetamol, opioids) are frequently ineffective. Bowsher [1] estimated that there are more than 550000 patients suffering from "neurogenic" pain conditions in the United Kingdom at any one time, equivalent to an incidence of 1%.

Clinical signs of neuropathic pain cover a wide range. There may be sudden shooting pain. Sharp pains may be felt at the point of mechanical stimulation and in peripheral or proximal locations. There may be continual burning pain. Light mechanical or thermal stimuli are often felt as painful (allodynia). Noxious stimuli may be appreciated as more painful than in non-affected tissues (hyperalgesia). In addition, there may be a delayed, increasing and spatially extended response to often innocuous stimulation (hyperpathia).

There is a strong bias towards the skin senses in our present understanding of neuropathic pain conditions. Further work is needed in order to assess the role of the visceral senses.

Physiologically, neuropathic pain differs from nociceptive and idiopathic pain, which are the two other categories of chronic pain [2]. Nociceptive pain is caused by stimulation of peripheral nociceptors. Neuropathic pain conditions are caused by mechanical trauma, ischaemia, degeneration or inflammation of the peripheral or central pain pathway. Invariably, this leaves the target tissue in a state of reduced and abnormal sensory potential. Even following optimal regeneration after transection of a peripheral nerve, a considerable number of nerve fibres make faulty connections [3], frequently causing development of areas of skin with discretely intermingled spots of numbness, normal tactile sensitivity and tactile allodynia [4]. Lindblom and Verillo [5] have described a typical increase in the range between warm and cold thresholds in patients suffering from neuralgias.

Until recently, experimental work on neuropathic pain was restricted by the absence of an animal model; during the past five years two such models have become available. Bennet and Xie [6] developed the now widely used model in which loose ligatures of digestable suture material are placed around the sciatic nerve of the rat. These animals exhibit behavioural changes indicating chronic pain beyond the time of complete digestion of the suture. Hao and colleagues [7], using a method described earlier by Watson, Prado and Dietrich [8], irradiated the spinal cord of rats with an argon laser beam after prior systemic injection with the photosensitive substance, erythrosin. The strength of radiation chosen was non-destructive in the absence of erythrosin. These animals also developed behavioural signs of neuropathic pain. Recovery was enhanced significantly by previous treatment with the N-methyl-D-aspartate antagonist, MK-801.

Neuropathic pain is a general term. Without knowledge of the processes underlying the development of neuropathic pain, it is difficult to understand the range of therapeutic measures used today. What are the specific mechanisms responsible for this most unpleasant condition? Recent clinical and basic science studies have provided several answers to this question.

Peripheral nerves respond to trauma with growth processes in the periphery and in the central terminals of affected primary afferent neurones. In a transected and resutured nerve there are, as pointed out above, a considerable number of incorrectly connected cutaneous sensory receptors [3]. Centrally, large fibres with touch receptors in the periphery may send sprouts towards lamina II in the dorsal horn, making synaptic contact with cells there which are normally targeted only by small-diameter, afferent C-fibres [9]. A synaptic connection of this nature provides new access to the pain pathway, devoid of any presynaptic inhibition normally modulating the input from nociceptors. Clinically, this abnormal nervous connection may be expected to cause allodynia. Furthermore, cutaneous nociceptors may become sensitized so that they respond to innocuous stimulation with touch, cold or warmth [10]. Regenerating peripheral nerve fibres may become spontaneously active [11]. They have been shown also to become sensitive to exposure to catecholamines [12]; Devor and Janig [13] demonstrated direct excitation of primary afferent nerve fibres in an experimental neuroma by stimulation of the sympathetic trunk which could be abolished by alpha-adrenergic block. Roberts [14] postulated that simultaneous sensitization to activity in the sympathetic nervous system of primary afferent fibres in the periphery and wide dynamic range neurones in the dorsal horn is the physiological basis of sympathetically maintained pain.

In clinical medicine there is considerable confusion about the role of the sympathetic nervous system in chronic pain. The term "sympathetically maintained pain" implies a chronic pain condition that can be abolished or much reduced by alpha-adrenoceptor blockade—for example with phentolamine [15, 16]. However, the term "reflex sympathetic dystrophy", covers such a large range of clinical signs that a working party at the last International Congress for the Study of Pain in 1990 could agree only on a very non-specific definition, stating specifically that the word "sympathetic" should not be taken to indicate a pathophysiological mechanism [17].

The above pathophysiological mechanisms should not be perceived as functioning in isolation. A clinically presenting pain is likely to be made up of several interacting components, some being more important than others [18].

Central neurones in the pain pathway are under powerful control of serotoninergic and catecholaminergic descending inhibitory neural pathways, originating from the brainstem [19]. The efficacy of these systems can be enhanced dramatically by relatively small doses of tricyclic antidepressant drugs [20, 21], presumably through inhibition of the re-uptake of transmitter substances [22].

Opioid sensitivity is a topic much researched in relation to neuropathic pain. Arner and Meyerson [2] found non-responsiveness in patients with neuropathic pain. To some extent, this result was a self-fulfilling prophecy, because the patients tested had been selected for spinal cord stimulation; these patients would have been pretested for all other, less invasive forms of treatment, with negative results. The authors did not attempt to treat their patients with doses of increasing strength (titration). In contrast Rowbotham, Reisner-Keller and Fields [23] observed some patients, suffering from post-herpetic neuralgia, who experienced partial or complete pain relief during titration with opioids. Portenoy, Foley and Inturrisi [24] pointed out that there is a continuum from insensitivity to complete sensitivity to opioids. Some theoretical reasons for opioid insensitivity are psychogenic pain, loss of post-synaptic receptor sites for opioids, possibly as a consequence of degeneration of endorphinergic or enkephalinergic inhibitory interneurones, or formation of new central nervous pathways bypassing inhibitory interneurones. All these processes could be partial and need not be complete. The unpredictability of a positive therapeutic response to opioids creates a dilemma, because it is inevitable that some patients become dependent with the possibility of not even gaining pain relief. This problem has recently been overcome by "titration dosing" of patients using a patient controlled analgesia device [25]. With this method, it appears to be possible to assess opioid sensitivity within a few hours—a time span too short for dependence to develop.

Lesions of other parts of the brain, not only the thalamus, may produce chronic pain [26]. It is therefore often more appropriate to refer to "central" than to "thalamic" pain. Therapeutically, this condition may respond well to treatment with tricyclic antidepressant or antiepileptic drugs [27]. Not uncommonly, central pain is a complication of cerebrovascular infarction. It may be misdiagnosed, particularly if there are spastic contractures in the painful part of the body.

In conclusion, the diagnosis "neuropathic pain" has lost some of its "black box" character during recent years, and therapy is beginning to be designed according to our increasing understanding of the pathophysiology of this condition.

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ORIGINAL ARTICLES

AWARENESS DURING TOTAL I.V. ANAESTHESIA

R. SANDIN AND O. NORDSTRÖM

SUMMARY

Five cases of awareness have been identified during total i.v. anaesthesia with mechanically controlled ventilation and neuromuscular block. Two of the cases resulted from inability to deliver the target dose of anaesthetics, while the patient's need for anaesthetics was greater than anticipated in three. It is concluded that all cases were caused primarily by lack of experience, and could have been prevented. These five cases occurred in experience from approximately 2500 patients anaesthetized with this technique. Pre-, per- and postoperative data on the most recent 1727 patients have been entered into a database and may serve to provide data on the group of patients in whom the five cases of awareness occurred. (Br. J. Anaesth. 1993; **71**: 782–787)

KEY WORDS

Anaesthetics, intravenous: propofol. Analgesics: alfentanil. Complications: awareness.

Awareness and subconscious learning during anaesthesia have been addressed in several recent papers. Previous studies of awareness have indicated an incidence of 1–4% in most types of surgery, but considerably greater incidences have been described in cardiac, trauma and obstetric surgery [1]. In a recent study on the incidence of awareness associated with currently used anaesthesia techniques, Liu and colleagues found two cases in 1000 patients [2]. As it is generally agreed that awareness occurs mainly with anaesthetic techniques using neuromuscular block [1], it may be appropriate to interpret these results as two cases of awareness in 684 patients who had been given neuromuscular blockers [2]. In that study the type of anaesthesia was not reported.

The incidence of awareness during total i.v. anaesthesia (TIVA) has not been investigated, but there are surprisingly few case reports of this complication associated with TIVA [3–5]. TIVA based on alfentanil (fentanyl in a few cases) and propofol was introduced at our hospital in 1989. Since then, there have been approximately 2500 cases of TIVA (without nitrous oxide) using mechanically controlled ventilation and neuromuscular block. Initially all patients were asked if they had "slept well" immediately after anaesthesia. However, the most recent 1727 patients have also been questioned on a second occasion about recall of intraoperative events. Five cases of awareness during TIVA have been identified.

PATIENTS AND METHODS

Patient No. 1

A 50-yr-old woman with epileptic seizures, breast cancer with cutaneous and intrapleural metastases and broncho–pleural fistulae was jaundiced because of obstruction and it was planned to insert a catheter percutaneously in order to drain bile. Her daily medication included more than 180 mg of morphine, diazepam, carbamazepine and dixyrazine. Her weight was 60 kg. She requested general anaesthesia for the procedure and it was decided to avoid nitrous oxide as she was considered to be at risk for pneumothorax. She refused any i.m. premedication and it was decided to give diazepam 20 mg rectally as premedication. Anaesthesia was induced 30 min later with fentanyl 0.2 mg and propofol 100 mg. Tracheal intubation was facilitated with vecuronium 5 mg. A continuous infusion of propofol at a scheduled rate of 600 mg h^{-1} (60 ml h^{-1}) was started. However, in the poor lighting in the x-ray department it was not noticed that, although the digits on the display of the Terumo infusion pump are illuminated, this is not the case for the decimal point indicating tenths of millilitres. Thus instead of 60 ml h^{-1}, the patient received 6.0 ml h^{-1}. Heart rate (HR) increased from 80 to 115 beat min^{-1} and the erroneous infusion rate was discovered; a simultaneous increase in systolic arterial pressure (SAP) was less pronounced. Immediately after tracheal extubation, the patient declared that she had been awake for a short period, but had not felt any pain. The mistake was explained to the patient approximately 1 h after tracheal extubation and she stated that she was satisfied and felt confident in the event of future anaesthetics. On the following day, the patient's attitude to the events had not changed.

Patient No. 2

A 35-yr-old woman was anaesthetized for laparoscopic tubal ligation. Her weight was 63 kg, height 1.76 m and haemoglobin 14.2 g dl^{-1}. Premedication was given 80 min before induction of anaesthesia and comprised ketobemidone 5 mg (Ketogan, Lundbeck A/S, Copenhagen, Denmark) (not available in the U.K.; ketobemidone 5 mg is equipotent to morphine 5–8 mg [6]) and dixyrazine 10 mg (Esucos, UCB, Bruxelles, Belgium) given i.m. An i.v. dose of glycopyrronium 0.2 mg was followed

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TABLE I. *Routine method for TIVA*

Without concomitant regional block	
Premedication	Ketobemidone 0.05–0.1 mg kg^{-1}+ dixyrazine 0.15 mg kg^{-1} i.m.
Anticholinergic	Glycopyrronium 0.2 mg (adults)
Induction	Vecuronium 0.01 mg kg^{-1} Alfentanil 1 mg min^{-1} until the patient responds slowly or not to commands (usually 25–50 μg kg^{-1})
	Propofol 1 (1.5) mg kg^{-1}
	Additional vecuronium to 0.07–0.1 mg kg^{-1}
	An infusion consisting of alfentanil 5 mg (10 ml) mixed in propofol 500 mg (50 ml); total volume 60 ml is started at a rate of: 1.0 ml kg^{-1} h^{-1} for 10 min; 0.8 ml kg^{-1} h^{-1} for 10 min; 0.6 ml kg^{-1} h^{-1} for 10 min, thereafter adjusted to clinical signs and anticipated demand. Smallest doses: < 60 yr 0.5 ml kg^{-1} h^{-1}; $\geqslant 60$ yr 0.4 ml kg^{-1} h^{-1}.
	In case of increases in SAP or HR indicative of light anaesthesia at any time in the above scheme, 5 ml of the mixture and 0.5 mg of alfentanil are injected and infusion rate is increased by 20%.
With concomitant regional block	
	Only 2.5 mg of alfentanil is added to propofol 500 mg. Infusion rates as above. Smallest infusion rates: < 60 yr 0.4 ml kg^{-1} h^{-1}; $\geqslant 60$ yr 0.3 ml kg^{-1} h^{-1}.

by alfentanil 2.5 mg and propofol 120 mg. An infusion of a mixture of propofol and alfentanil (100 mg:1 mg) was started (the infusion rate was not noted in the anaesthesia record). Intubation of the trachea was facilitated with vecuronium 6 mg. Additional doses of vecuronium 2 mg and alfentanil 0.5 mg were given when surgery started. The anaesthesia record is difficult to interpret and timing of events may not be correct. However, it is clear that marked increases in HR and SAP were evident. It is also clear that the recorded volume of infused anaesthetic mixture during the procedure (corresponding to average doses of propofol 4.6 mg kg^{-1} h^{-1} and alfentanil 46 μg kg^{-1} h^{-1}) was surprisingly small—the amounts of anaesthetics were 23% less than the smallest recommended dose in our infusion scheme used at that time (table I). It has not been possible to determine if the decreased dosing was caused by erroneous calculation of required doses or if the infusion pump or venous catheter functioned incorrectly in addition to insufficient administration of drugs in response to vital signs.

Antagonism of neuromuscular block was attempted immediately after surgery (glycopyrronium 0.5 mg+neostigmine 2.5 mg). However, residual effects of the neuromuscular block were evident after extubation and an additional dose of glycopyrronium and neostigmine (50% of the previous doses) was given. To start preparation for re-intubation of the trachea, midazolam 2.5 mg was given, but the ventilatory capacity suddenly improved. Immediately thereafter, the patient declared that she had been awake during a part of the procedure. She had noted the tracheal tube and had felt slight abdominal pain or, rather, discomfort. The duration of awareness could not be determined. However, it clearly took place during surgery. The situation was discussed with the patient 2 h after surgery and also the following day. She was encouraged to request another consultation if late symptoms ensued, but no further contact was made.

Patient No. 3

A 37-yr-old female suffering from vesico–ureteral reflux underwent reimplantation of the right ureter. No renal impairment or other medical illness was evident. Cosmetic breast surgery had been performed 2 months earlier. Her weight was 60 kg and her height 1.73 m. Premedication consisted of dixyrazine 10 mg p.o. given 290 min before induction and an i.m. injection of ketobemidone 3.75 mg 100 min before induction. An i.v. dose of glycopyrronium 0.2 mg was followed by alfentanil 2.5 mg and propofol 100 mg. Infusion of a mixture of propofol and alfentanil (100 mg:1 mg) was started at a rate corresponding to propofol 8 mg kg^{-1} h^{-1} and alfentanil 80 μg kg^{-1} h^{-1} (table I). Intubation of the trachea was facilitated with vecuronium 6 mg. The venous cannula was accidently pulled out when the patient was placed in the left lateral position and was not easy to re-insert. This took approximately 5 min. Immediately before a rapid infusion of anaesthetics was given, the surgeon's assistant entered the theatre and made an appreciative remark about the results of the previous plastic surgery. After tracheal extubation, the patient immediately announced that she had heard the assistant's comment. No other input was recalled, but she had understood her situation perfectly well. She had found the situation amusing and not at all unpleasant. This opinion persisted on the following day. No alterations in HR and SAP were found in the anaesthesia record which corresponded to the period when awareness occurred.

Patient No. 4

A 29-yr-old woman underwent laparoscopy because of infertility. She had suffered from decreased arterial pressure and occasional orthostatic reactions. No other disease was indicated in the medical history. Her weight was 50 kg, her height 1.67 m, and her haemoglobin concentration 13.3 g dl^{-1}. Premedication was given 65 min before induction and consisted of i.m. injections of ketobemidone 5 mg and dixyrazine 10 mg. An i.v. dose of glycopyrronium 0.2 mg was followed by alfentanil 2.5 mg and propofol 80 mg. Infusion of a mixture of propofol and alfentanil (100 mg: 1 mg) was started at a rate corresponding to propofol 8 mg kg^{-1} h^{-1} and alfentanil 80 μg kg^{-1} h^{-1} (table I). Intubation of the trachea was facilitated with vecuronium 4 mg. The surgeon was called for an emergency case, and the operation was not started until 55 min after induction. In the meantime, SAP and HR remained unchanged, and the infusion of propofol and alfentanil had been reduced gradually to 4 mg kg^{-1} h^{-1} and 40 μg kg^{-1} h^{-1}, respectively. This infusion rate was continued for 15 min. Immediately before the start of surgery the infusion rate was increased by 20%, and an additional dose of vecuronium 2 mg given. Catheterization of the bladder, introduction of the instrument for intra-uterine injection of methylene blue and introduction of the needle for i.p. insufflation of carbon dioxide were not followed by any response in SAP or HR. After i.p. insufflation of carbon dioxide and a head-down tilt, SAP increased by 10 mm Hg, to that recorded before anaesthesia; and HR remained unchanged, at 55 beat min^{-1}. Introduction of the trochar, however, was followed by a sudden increase in HR to 90 beat min^{-1} and an additional increase in SAP to 110 mm Hg. At this time, approximately 10 min after the start of the operation, the infusion rate of the anaesthetic mixture was increased to propofol 6.4 mg kg^{-1} h^{-1} and alfentanil 64 µg kg^{-1} h^{-1}, and an additional dose of vecuronium 2 mg was given. The patient was then given terbutaline 0.25 mg i.v. for relaxation of the uterus and HR increased further to 130 beat min^{-1} and SAP to 120 mm Hg. Surgery was completed 10 min later. Neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrronium 0.5 mg. The patient regained consciousness 5 min after the anaesthetic mixture was discontinued and communicated, immediately after extubation of the trachea, that she had been awake. An initial interview was repeated 2 h later, and revealed that the patient remembered something pressing against her belly. She could also relate what the anaesthesia nurse had done in that situation. Thus it could be established that the patient had been conscious for a short period during the introduction of the trochar, corresponding to the increase in HR from 55 to 90 beat min^{-1}. No memories were recalled after that. The patient expressed that she was satisfied with the explanation of what had happened. The situation was explained once again on the following day.

Patient No. 5

A 52-yr-old woman underwent anterior resection because of malignant tumour of the sigmoid colon. She was sensitive to aspirin. No other disease was indicated in the medical history. Her weight was 75 kg, her height 1.63 m, and her haemoglobin concentration 13.0 g dl^{-1}. The patient had not been scheduled for surgery until the evening before, and therefore no preoperative visit had taken place and there was no order for premedication. In the anaesthesia room the patient was given fentanyl 0.05 mg i.v. and an extradural catheter was placed at the L2–3 interspace. Plain 0.5% bupivacaine 11 ml provided an upper sensory level of T4. The patient was rather anxious and 20 min later she was given an i.v. dose of midazolam 1.25 mg. A decrease in SAP was treated by i.v. injection of ephedrine 5 mg. Because of a delay in the theatre, scheduled general anaesthesia was not induced until 80 and 60 min after the i.v. doses of fentanyl and midazolam, respectively. Anaesthesia was induced with alfentanil 2.5 mg and propofol 40 mg, followed by infusion of a mixture of propofol and alfentanil (200 mg:1 mg) started at a rate corresponding to propofol 23 mg min^{-1} and alfentanil 110 µg min^{-1}. When the patient no longer responded to verbal command and no eyelid reflexes were evident, vecuronium 7 mg was given (the total dose of propofol at this time is not known). Tracheal intubation was attempted after an additional dose of alfentanil 0.5 mg, but was difficult and several attempts were required. Approximately 10 min elapsed before the tracheal tube was in place. (There were some difficulties in the adjustment of the anaesthetic infusion because the technical assistant was not sufficiently familiar with the infusion pump. The significance of this is not known.) The recordings of HR and SAP during this period were few and the timing may not be correct. HR 120 beat min^{-1} was observed on the monitor by the anaesthetist who was called to aid with the intubation (HR 70 beat min^{-1} before induction). After tracheal intubation, the anaesthetic infusion was reduced to propofol 7.8 mg kg^{-1} h^{-1} and alfentanil 39 µg kg^{-1} h^{-1}. Immediately after tracheal extubation the patient declared that she remembered a painful sensation in her throat, but nothing after that. From her description it could be established that she had experienced the tracheal intubation. This patient wanted to talk about what had happened on four occasions, the last time being 7 days after surgery. She had no nightmares, but wanted to "get it out of her system". She was offered additional contact, but said that she felt relieved after the last consultation. It was confirmed 3 weeks later that this patient had recovered well mentally.

TABLE II. *Data on 1727 patients anaesthetized with TIVA (number, median [range] or mean (SD) [range])*

Men:women	644:1083
Ambulatory surgery (%)	13
Age (yr)	41 [2–92]
Duration of surgery (min)	68 [2–708]
End of surgery–extubation (min)	11.5 (8.4) [0–70]
Stay in PCU (h)	2.3 [0–9.9]
Use of naloxone (%)	0.9
Concomitant extradural block (%)	16

Patient data

Our routine at the time when TIVA was introduced was to ask all patients after extubation if they had "slept well" (approximately 800 TIVA in that period). It has become our practice since April 15, 1991, to enter into a database pre-, per- and postoperative data on all patients anaesthetized in our department. This report is based on all patients for whom details were entered in the database at March 1, 1993 (anaesthetized up to February 24, 1993).

The occurrence of awareness has been a major concern in the collection of data. Thus the most recent 1727 patients were also questioned on a second occasion, when they left the postoperative care unit (PCU), about their opinion of the anaesthesia and whether "any unpleasant experiences during anaesthesia" have been evident. Reliable answers were obtained from 83% of these patients. Data from the 1727 patients anaesthetized after the questioning about awareness had been extended are summarized in table II.

In this report "TIVA" refers only to those procedures involving muscle relaxation and mechanically controlled ventilation.

In patient No. 1, arterial pressure was recorded manually by means of a calibrated mercury column. In patients Nos 2–5 automatic non-invasive arterial pressure (every 5 min) and heart rate were displayed by means of a Hewlett–Packard 1092A monitor and written manually into the anaesthesia record.

DISCUSSION

Factors thought to be of relevance to the occurrence of awareness in the five patients described are summarized in table III.

Organization

The organization of anaesthesia service may require some comment, as it seems probable that an experienced and vigilant anaesthetist would have been able to prevent all five cases of awareness (table III).

In Sweden and the Scandinavian countries, anaesthesia is administered frequently by anaesthesia nurses [7]; in our department they are allowed to induce (including tracheal intubation), maintain and terminate general anaesthesia in ASA I–II patients. Each senior anaesthetist is responsible for supervision of approximately four simultaneous cases (The Swedish Anaesthetists Association recommends a maximum of two simultaneous anaesthetics). The anaesthetist must always be immediately available for consultation, help and performance of certain procedures.

Awareness in relation to the introduction of a new anaesthesia technique

As TIVA is based on administration of anaesthetics via an infusion pump instead of a vaporizer, this requires special considerations. Understanding of pharmacokinetics is essential, as the effects of propofol and alfentanil are terminated rapidly by redistribution and elimination, and interindividual variability is great. Despite the fact that methods for detection of awareness have not been described, it seems that awareness can be avoided when TIVA is administered by highly qualified anaesthetists [8]. However, introduction of this technique into widespread clinical practice may be more complicated. When TIVA was introduced in our hospital, an anaesthetist experienced in this technique attended or supervised all patients closely. This was no longer possible after approximately the first 500 cases, as the method was considered to be advantageous in some cases and the number of TIVA increased. This increased use of TIVA was associated with four cases of awareness (patients Nos 1–4) within 8 months (739 TIVA were performed in that period). It may be argued that all five cases of awareness could have been prevented if there had been better knowledge about technical equipment (patient No. 1, possibly patient No. 5), pharmacokinetics (patients Nos 2–5) and the importance of observing and responding to vital signs (patients Nos 2, 5). The number of TIVA conducted by the anaesthesia nurse before a case of awareness occurred (patient No. 1: $n = 2$; patient No. 2: $n = 16$; patient No. 3: $n = 47$; patient No. 4: $n = 17$; patient No. 5: $n = 52$) may support the assumption that lack of experience was a major factor in at least some instances. An alternative view is to regard these events as indicative of an insufficient number of anaesthetists in the organization, insufficient supervision by the responsible anaesthetist, or both. However, this does not constitute evidence that all cases could have been prevented simply by replacing the anaesthesia nurse with an anaesthetist—an anaesthetist who was rather unfamiliar with TIVA attended patient No. 1. During the past year, only one case (patient No. 5) of awareness has occurred (925 TIVA procedures with neuromuscular block) despite the fact that anaesthesia nurses have administered the majority of TIVA. In addition to the increasing experience that comes with conducting a greater number of cases, an important reason for the seemingly decreasing incidence of awareness in our department may be that every case of awareness has been publicized to all anaesthesia nurses and anaesthetists and appropriate routines introduced.

TABLE III. *Probable reasons for, and factors contributing to, awareness*

Patient No. 1	Erroneous setting of the infusion pump. Insufficient premedication?
Patient No. 2	Too small doses of anaesthetics; insufficient dosing in response to clinical signs.
Patient No. 3	No infusion of anaesthetics. Reduced effect of premedication?
Patient No. 4	Insufficient doses of anaesthetics when noxious stimulation began after dosing had been adjusted in response to a low degree of stimulation.
Patient No. 5	No additional bolus doses during prolonged intubation; insufficient dosing in response to clinical signs. Insufficient technical assistance. Insufficient premedication.

Vital signs in TIVA

It is interesting to note that awareness was associated with marked increases in HR and SAP in patients Nos 1, 2, 4 and 5. The increases in HR were generally more distinct than those for SAP when compared with preanaesthetic values. The reason that no changes in vital signs were observed in patient No. 3 may have been that noxious stimulation was minimal and this patient found the period of awareness amusing rather than unpleasant. It has been suggested that, if no pain is evident, mental distress during awareness is necessary to evoke a response in vital signs [9].

There are three previous case reports on awareness or wakefulness during propofol anaesthesia [3–5]. A continuous infusion of alfentanil was not used in any of these patients. An increase in HR from 82 beat min^{-1} before anaesthesia to 122 beat min^{-1} with hypertension was found in the patient described by Kelly and Raymond (no opioid) [3]. The patient described by Schäfer and Marsch (alfentanil 25 $\mu g\ kg^{-1}$ as bolus at induction) felt that he was suffocating and an increase in SAP was evident during insertion of the Kleinsasser laryngoscope. This was followed by SAP and HR slightly greater than the values before anaesthesia [5]. In a case of wakefulness without recall described by Rupreht (fentanyl 0.2 mg > 45 min before the wakefulness), "none of the monitored variables changed" (the type of monitoring is not described) [4]. Thus in five of the seven cases of awareness during propofol anaesthesia without nitrous oxide described to date, a marked increase in HR was observed. If the cases of awareness which occurred during noxious stimulation or which were associated with possible mental distress are considered, two of three patients (our patient No. 1 and one from each of references [3] and [5]) have responded with an increase in HR when an infusion of alfentanil was not used, whereas awareness during painful stimulation was associated with an increase in HR in all three patients given a continuous infusion of alfentanil (our patients Nos 2, 4, 5).

Despite the fact that it is generally agreed that vital signs may be fallible as indicators of impending awareness [1], this has not been investigated for TIVA. The value of HR as an indicator of impending awareness may differ for different drug combinations [10]. Propofol, alfentanil and vecuronium have minimal or no vagotonic action when administered singly [11, 12], but in combination, these drugs have a pronounced vagotonic action and a stable, moderately slow HR is common during most types of non-cardiac surgery.

It may have been expected that vital signs would be less obvious in the elderly because of an increased prevalence of cardiac disease and medication interfering with the sympathetic nervous system, thus making dose requirements more difficult to estimate. However, no case of awareness in a subject older than 52 yr has been identified, despite the fact 33% of patients were older than this, cardiovascular disease was evident in 36%, and an abnormal ECG was found in 26% of the patients in this subgroup.

Method for detection of awareness

Many patients are reluctant to discuss awareness spontaneously [1]. In order to detect awareness, patients should therefore be interviewed to elicit this complication. The interview should probably be performed within 2–3 days after surgery [1]. An example of correct questioning has been described by Brice, Hetherington and Utting [13]. Our routine at the time when TIVA was introduced was to ask all patients after extubation if they had "slept well". Despite the fact that many patients seem clear-headed immediately after TIVA, this interview may not be sufficient. After approximately 800 TIVA had been performed, we changed our routine, and since then all patients are also questioned when they leave the PCU about their opinion of the anaesthesia and whether "any unpleasant experiences during anaesthesia" had been evident. The results of this questioning are documented in the medical record. According to Adam, even this time of questioning may be too soon after anaesthesia [14]. For inhalation agents, memory of verbal material may be better after 1 week than after 2 h [14]. This has not been investigated for propofol and alfentanil. However, we have found it difficult to question the patient after he has left the PCU. Thus we cannot guarantee that we have identified all cases of awareness, especially not before the additional questioning was introduced. However, despite the fact that all five cases of awareness were identified after the questioning had been extended, all these patients communicated their awareness immediately after extubation and no case of awareness during TIVA has remained undiscovered until the second questioning. The two previously described patients with recall of intra-operative events after propofol anaesthesia were also capable of communicating their experiences immediately after anaesthesia [3, 5]. This may indicate that, provided no dramatic and unreported improvement in recall took place several hours after propofol anaesthesia, the number of undiscovered cases of awareness among the first 800 patients (approximately) was small. Nevertheless, a prospective study is necessary in order to establish the incidence of awareness with TIVA. It should be noted also that, as discussed previously, these cases occurred during a period when the TIVA technique was introduced into routine practice and may therefore reflect a temporary lack of experience.

Dose regimen and mixture vs *separate infusions of alfentanil and propofol*

A mixture of alfentanil and propofol was used in patients Nos 2–5. Our initial dose regimen used in patients Nos 2–4 is given in table I. At the time when the fifth case of awareness occurred, a modified scheme had been introduced in order to avoid underdosing light, young patients, to avoid overdosing elderly patients, to obtain an idea of the individual dose requirements and to reduce the effect of propofol on SAP because of the hysteresis effect [15] (doses are calculated according to lean body mass; 1% reduction of doses for every year > 45 yr; induction with a bolus dose of propofol 0.5 mg kg^{-1} followed by an initial rapid infusion). Fewer than 10% of TIVA procedures in our department have been performed with separate infusions. In addition to the initial study of a mixture of alfentanil and propofol published by Kay in 1986 [16], there are now two studies [17, 18] and one report of four patients [19] indicating that the pharmacodynamics of alfentanil and propofol are not altered if they are administered as a mixture instead of separate infusions. Despite the fact that, in some situations, it may be desirable to be able to alter the relative amounts of alfentanil and propofol [8], the cases presented provide no evidence that infusion of a mixture of alfentanil and propofol increased the risk of awareness compared with separate infusions. Furthermore, awareness and wakefulness have also occurred with large infusion rates of the hypnotic component, propofol [3–5].

CONCLUSION

All five cases of awareness during TIVA must be considered as having been avoidable with experience and vigilance. Despite the fact that the five patients do not provide any answers on incidence of awareness in TIVA, reliability of vital signs, optimal time for postanaesthesia interview, or the risk for persisting neurotic symptoms, they may provide useful hints for future studies of these factors. Because of the low incidence (for scientific purposes) of awareness, reliance is often placed on case reports. Therefore, all cases of awareness in TIVA should, in our opinion, be published in detail and a judgement should be made as to whether or not information in the anaesthesia record (timing of events and haemodynamic responses) is reliable.

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RE-EXPANSION OF ATELECTASIS DURING GENERAL ANAESTHESIA: A COMPUTED TOMOGRAPHY STUDY

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SUMMARY

*Formation of atelectasis is one mechanism of impaired gas exchange during general anaesthesia. We have studied manoeuvres to re-expand such atelectasis in 16 consecutive, anaesthetized adults with healthy lungs. In group 1 (10 patients), the lungs were inflated stepwise to an airway pressure (*Paw*) of 10, 20, 30 and 40 cm H_2O. In group 2 (six patients), three repeated inflations up to* Paw = *30 cm H_2O were followed by one inflation to 40 cm H_2O. Atelectasis was assessed by analysis of computed x-ray tomography (CT). In group 1 the mean area of atelectasis in the CT scan at the level of the right diaphragm was 6.4 cm^2 at* Paw *= 0 cm H_2O, 5.9 cm^2 at 20 cm H_2O, 3.5 cm^2 at 30 cm H_2O and 0.8 cm^2 at 40 cm H_2O. A* Paw *of 20 cm H_2O corresponds approximately to inflation with twice the tidal volume. In group 2 the mean area of atelectasis was 9.0 cm^2 at* Paw *= 0 cm H_2O and 4.2 cm^2 after the first inflation to 30 cm H_2O. Repeated inflations did not add to re-expansion of atelectasis. The final inflation (*Paw *= 40 cm H_2O) virtually eliminated the atelectasis. We conclude that, after induction of anaesthesia, the amount of atelectasis was not reduced by inflation of the lungs with a conventional tidal volume or with a double tidal volume ("sigh"). An inflation to vital capacity (*Paw *= 40 cm H_2O), however, re-expanded virtually all atelectatic lung tissue.* (Br. J. Anaesth. 1993; **71**: 788–795)

KEY WORDS

Anaesthesia: general. Complications: atelectasis. Lung: atelectasis, gas exchange. Ventilation: mechanical.

It is well known that general anaesthesia impairs pulmonary gas exchange [1]. Much effort has been spent in analysing possible mechanisms, and 30 years ago the concept of progressive alveolar collapse during general anaesthesia with mechanical ventilation was put forward by Bendixen, Hedley-Whyte and Laver [2]. Atelectasis has been demonstrated in more recent studies, although the mechanism appears to differ from that which had been suggested initially. Thus, loss of respiratory muscle tone causing reduction in functional residual capacity and compression of dependent parts of the lungs was proposed, rather than absorption of gas behind closed airways [3]. A correlation has been shown between atelectasis and the magnitude of shunt [4, 5]. It is not known if the amount of atelectasis may be reduced by passive inflations of the lungs and at what extent of inflation this occurs.

The purpose of this study was to estimate, in anaesthetized subjects with healthy lungs, the change in the amount of atelectasis during inflations of the lungs up to a volume equal or close to vital capacity.

PATIENTS AND METHODS

Informed consent was obtained from each patient and the study was approved by the Ethics Committee of the University Hospital of Uppsala. We studied 16 consecutive patients (age range 28–61 yr; seven female) (table I) undergoing elective neurosurgical procedures or laparoscopic surgery. No patient had cardiac or pulmonary disease. Patients were allocated to group 1 (recruitment manoeuvre by stepwise inflation) or group 2 (recruitment manoeuvre by repeated, similar inflations).

Anaesthesia

No premedication was given. Anaesthesia was induced with propofol 2 mg kg^{-1} and fentanyl 1–2 µg kg^{-1} i.v., followed by a continuous infusion of propofol 3–5 mg kg^{-1} h^{-1}. Patients received pancuronium 0.1 mg kg^{-1} to facilitate tracheal intubation; additional doses of 1–2 mg were given when needed. The lungs were ventilated mechanically at a rate of 10 b.p.m. with 60 % nitrogen in oxygen (Servo Ventilator 900D or 710, Siemens). The end-inspiratory pause was set at 0.6 s and the end-expiratory pressure was 0 cm H_2O (= ZEEP). Total ventilation was adjusted to maintain an end-expiratory carbon dioxide concentration of approximately 4 % (CO_2 Analyzer Eliza, Engström). Ventilatory volumes and airway pressures were obtained from the ventilator. The total dynamic compliance of the respiratory system (*C*rs) was calculated as tidal volume divided by end-inspiratory airway pressure.

Computed tomography of the chest

The densities of the lungs were studied by computed tomography of the lungs (Somatom plus, Siemens). The subjects were in a supine position

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TABLE I. *Patient characteristics (mean (range)). †Calculated from BMI = wt/ht² [6]; mean for all our subjects, 25.9 kg m^{-2}. (For comparison: BMI of white North American men and women (ages 42–44 yr) (25th percentile/mean/75th percentile): 23.4/25.8/28.3 kg m^{-2} and 21.5/23.8/28.0 kg m^{-2}, respectively [7])*

	Group 1	Group 2
n	10	6
Age (yr)	43 (28–61)	48 (40–59)
Sex (M/F)	6/4	3/3
Weight (kg)	75.7 (53–100)	80.7 (64–90)
BMI (kg m^{-2})†	24.9 (18.3–30.8)	27.7 (23.5–31.8)
Smokers	1	2

with the arms raised above the head. An antero–posterior scout view covering the chest was obtained at end-expiration, awake and after induction of anaesthesia. For each subsequent analysis, one CT scan in the transverse plane was performed at end-expiration, 0–1 cm above the top of the right diaphragm. In group 1, a second scan was taken 5 cm cranially. The scan time was 1 s, at 225 mA and 137 kV, with a slice thickness of 8 mm. Because the position of the diaphragm may vary between awake and anaesthesia, the scan levels relative to the spine were not identical.

To obtain slices from approximately the same lung region during the various inflations of the lungs, the scan was moved caudally, assuming a caudal movement of the diaphragm of 15 mm with each 10 cm H_2O increment of airway pressure (*P*aw). To verify the extent of movement, an additional antero–posterior scout view was performed at maximal inflation (*P*aw = 40 cm H_2O) in patients in group 1. The distance between the 4th or 5th lumbar spine and the top of the right and left diaphragm and the distance from the diaphragm to the apex of the lung were measured on each scout view and used to calculate the movement of the diaphragm.

To identify the densities (considered to reflect atelectasis), a magnified image (approximately × 2.5) was made of the dorsal portion of the CT scan of both the right and left lung. The dorsal border between the thoracic wall and the dense areas was drawn manually, but the ventral border between aerated lung tissue and atelectasis was identified by the region of interest program. The atelectatic area was calculated by the computer, including elements between −100 and +100 Hounsfield units (HU). The extent of atelectasis was expressed in absolute values (cm^2) and as a percentage of the total intrathoracic area (including the mediastinum) [4].

Ventilation/perfusion ratios and blood-gas analysis

The ventilation/perfusion ratios ($\dot{V}_A/\dot{Q}$) were assessed by the multiple inert gas technique [8]. Isotonic saline with a mixture of six inert gases (sulphur hexafluoride, ethane, cyclopropane, enflurane, diethyl ether and acetone) was infused into a peripheral vein at a rate of 3.5 ml min^{-1}. Under steady state conditions, arterial blood and mixed expired gas samples were collected in duplicate for subsequent analysis by gas chromatography. Oxygen uptake ($\dot{V}O_2$) was estimated using the Douglas-bag technique: expired gas was collected and mixed expired oxygen measured using a mass spectrometer. The cardiac output was estimated as $0.02 \times \dot{V}O_2$, assuming an arterio–venous oxygen content difference of 50 ml/litre of blood. Mixed venous inert gas concentrations were computed from the arterial values using mass balance principles [9]. This approximation of cardiac output is rather imprecise; however, it has been shown that the indices of $\dot{V}_A/\dot{Q}$ mismatch (SD of logarithmic perfusion distribution (log SDQ) and SD of logarithmic volume distribution (log SDV)) remain essentially unaffected by such uncertainties [9]. By mathematical analysis, the $\dot{V}_A/\dot{Q}$ distributions were fitted to a 50-compartment model. The result giving the best fit of data (smallest residual sum of squares (RSS)) of the duplicate samples was used for further statistical analysis. Perfusion of lungs with $\dot{V}_A/\dot{Q} < 0.005$ was defined as "shunt" and perfusion of lungs with $0.005 < \dot{V}_A/\dot{Q} < 0.1$ was defined as "low $\dot{V}_A/\dot{Q}$".

Arterial blood-gas tensions were measured using the ABL-2 (Radiometer). The alveolar–arterial oxygen partial pressure difference ($P_{A_{O_2}} - P_{a_{O_2}}$) was calculated according to:

$$(P_{A_{O_2}} - P_{a_{O_2}}) = F_{I_{O_2}} \times (P_B - P_{H_2O}) - (P_{a_{CO_2}}/RQ) - P_{a_{O_2}}$$

where P_B = barometric pressure; P_{H_2O} = water vapour pressure; RQ = respiratory quotient, assumed to be 0.8.

Lung volumes

In the awake, supine patient, the vital capacity was measured according to standard procedures. In the anaesthetized patient, we estimated the vital capacity by a procedure analogous to that used for airway closure during anaesthesia [10]. The lungs were inflated first to *P*aw 40 cm H_2O and then deflated to *P*aw −15 cm H_2O (BOC manometer, Ohmeda, attached to the tracheal tube). To avoid interference with the recruitment manoeuvre and with the estimation of atelectasis, this vital capacity recording was performed at the end of the measurement series for each individual patient. For all the above measurements, a Fleisch pneumotachograph (Godart, Einthoven Netherlands) was used.

Two or more measurements were made to obtain a minimum of two acceptable readouts and the mean of two or more readings was used for statistical analysis.

General procedure and recruitment manoeuvre

In the x-ray department, the infusion of inert gases was started and a catheter was inserted in a radial artery. The first CT scan and the measurement of vital capacity were then performed. After 40 min of infusion, samples were obtained for the gas exchange measurements. The patient was then anaesthetized. After 20 min of stable anaesthesia, gas exchange measurements and CT scans at end-expiration were repeated.

In the first 10 patients (group 1) a *stepwise inflation* of the lungs was performed (fig. 1): with a super-syringe, the lungs were inflated to *P*aw 10 cm H_2O. This pressure was held for about 15 s while the two CT scans were taken. This procedure was repeated subsequently with inflations to 20 cm H_2O, then

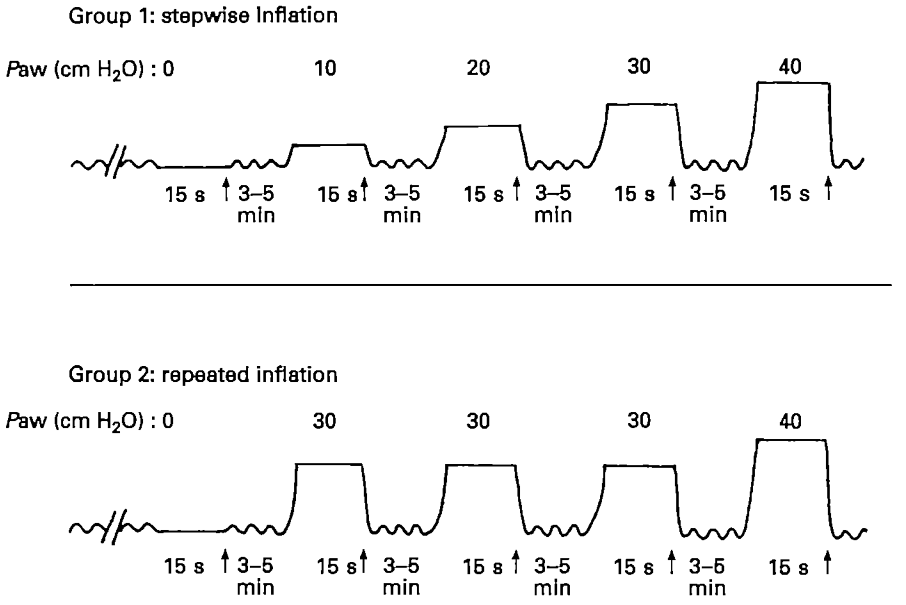

FIG. 1. Recruitment manoeuvre and timing of CT of the lungs (↑) (time intervals not to scale). Inflation to the various airway pressures maintained for 15 s.

30 cm H_2O and finally 40 cm H_2O. Between each inflation, the lungs were ventilated for 3–5 min at the baseline setting of the ventilator. As mentioned above, for each increment of 10 cm H_2O, the scan level was moved 15 mm caudally, and the position of the diaphragm at an inflation to 40 cm H_2O was checked with a final scout view. After the measurement of the "vital capacity anaesthetized", the patient was moved to the operating theatre.

In group 2 the lungs were inflated in a similar manner, but starting with three inflations up to 30 cm H_2O and finally with inflation to Paw 40 cm H_2O (fig. 1). Between inflations the lungs were ventilated for 3–5 min at the baseline setting of the ventilator. CT scans were taken at end-inspiration, as for group 1, but only the scan at the level of the diaphragm was performed in group 2. Finally, vital capacity anaesthetized was measured and the patient was moved to the operating theatre.

As it was not known in advance at which inflation a significant change in the extent of atelectasis would be attained, it was necessary to investigate the two groups sequentially. Thus a randomized procedure was precluded.

Statistics

Unless stated otherwise, mean values and SD are presented. Within each group, the significance of the difference between the atelectasis at different inflations was tested using Friedman two-way ANOVA and Wilcoxon's signed ranks test. Spearman's rank correlation and multiple stepwise linear regression were used to analyse relationships between different variables. For all calculations, the SYSTAT computer software package (SYSTAT, Evanston IL, U.S.A.) was used.

RESULTS

Awake

Overall, the measurements in the awake patients were in the normal range (table II).

Only two patients, one in each group, had a small amount of densities in the dependent part of the caudal scan. The CT scans displayed no other abnormalities.

The measured retention and excretion of the inert gases resulted in technically good ventilation/perfusion distributions. The fit of the ventilation/perfusion data, expressed as RSS, averaged 3.7 and did not exceed 6 in 13 of 16 measurements, thus fulfilling the criteria established by Wagner and West [11]. A small shunt up to 1% was found in three patients. The partial pressure of oxygen in arterial blood exceeded 10.0 kPa in all patients but one (overall mean 12.3 (1.9) kPa) and Pa_{CO_2} was in the normal range (mean 5.2 (1.0) kPa).

Anaesthesia

The main findings after induction of anaesthesia are summarized in table II. The intrathoracic area at the level of the diaphragm (scan 1) decreased by a mean of 4 (8)%. Fourteen patients developed atelectasis; the mean area was 7.0 cm^2 (mean of all 16 patients), corresponding to 2.1% of the total intrathoracic area. There was a correlation between body constitution as expressed by body mass index (BMI) and the extent of atelectasis (fig. 2).

Compared with the awake, supine position, the top of the left and right diaphragm moved cranially on average by 10 (11) mm ($P = 0.0002$, sign test) and 9 (11) mm ($P = 0.001$, sign test), respectively. The $\dot{V}A/\dot{Q}$ measurements were technically good with a greatest RSS of 4.5 and mean RSS 1.4. The increase in log SD$\dot{Q}$ from awake 0.78 to anaesthesia 0.95 reflects a broadening of the $\dot{V}A/\dot{Q}$ mode. The shunt (perfusion of regions with $\dot{V}A/\dot{Q} < 0.005$) increased in 13 patients (mean of all 16 patients: 6.6 (5.3)%) and an increase in low $\dot{V}A/\dot{Q}$ ($0.005 < \dot{V}A/\dot{Q} < 0.1$) was found in 11 patients (mean of 16 patients: 2.4 (2.4)%). In five patients, low $\dot{V}A/\dot{Q}$ decreased or remained unchanged, but in these patients the sum of shunt plus low $\dot{V}A/\dot{Q}$ increased with anaesthesia.

TABLE II. *Lung CT, lung mechanics and gas exchange data awake and during anaesthesia (mean (SD)). Scan 1 = at level of right diaphragm; scan 2 = 5 cm cranially.* V_T = *Tidal volume; VC = vital capacity (for details of VC measurement, see text);* Crs = *dynamic compliance of the respiratory system during mechanical ventilation; shunt* = $\dot{V}_A/\dot{Q} < 0.005$; *low* $\dot{V}_A/\dot{Q} = 0.005 < \dot{V}_A/\dot{Q} < 0.1$; *CO = cardiac output;* $(P_{A_{O_2}} - P_{a_{O_2}})$ = *alveolar–arterial oxygen partial pressure difference.* †*Median 3.3 cm², range 0–20.1 cm² (skewed data);* ††*median 1.5 cm², range 0–9.2 cm² (skewed data);* ‡*median 9.8 cm², range 5.1–12.0 cm² (skewed data); N.S. = not studied.* §*Movement of diaphragm in relation to position awake, supine: positive value = cranial movement.* *$F_{I_{O_2}}$ *awake = 0.21;* $F_{I_{O_2}}$ *anaesthesia = 0.40*

	Group 1		Group 2	
	Awake	Anaesthesia	Awake	Anaesthesia
Atelectasis scan 1 (cm²)	0.0 (0.1)	5.7†	0.0 (0.1)	9.0‡
Atelectasis scan 2 (cm²)	0.0 (0.0)	2.0††	—	N.S.
Diaphragm left (mm)§	—	10 (12)	—	10 (10)
Diaphragm right (mm)§	—	9 (13)	—	8 (7)
V_T (ml kg^{-1})	—	9 (1.1)	—	9 (1.5)
VC (litre)	3.9 (0.8)	4.1 (0.8)	3.7 (0.7)	3.5 (0.7)
Crs (ml cm H_2O^{-1})	—	75 (19)	—	60 (15)
Shunt (%CO)	0.0 (0.1)	4.7 (4.7)	0.2 (0.5)	9.9 (4.8)
low $\dot{V}_A/\dot{Q}$ (%CO)	1.8 (2.4)	3.0 (2.9)	1.1 (2.5)	1.6 (1.0)
$(P_{A_{O_2}} - P_{a_{O_2}})$ (kPa)*	0.9 (1.9)	10.3 (7.5)	1.4 (0.6)	15.9 (5.5)

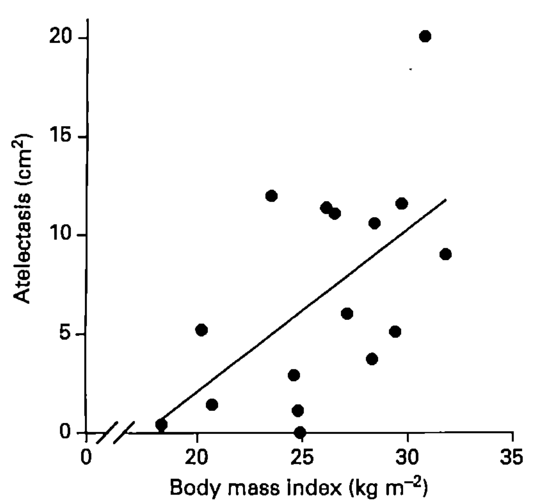

FIG. 2. Atelectatic area during anaesthesia and body mass index. $r = 0.66$; $P = 0.010$.

There was a correlation between shunt and atelectatic area ($r = 0.66$, $P = 0.006$).

At $F_{I_{O_2}}$ 0.4, mean arterial oxygen partial pressure was 19.6 (7.4) kPa.

Stepwise inflation (group 1)

During stepwise inflation, the extent of atelectasis decreased significantly only at airway pressures of 30 and 40 cm H_2O (table III, fig. 3). At *P*aw 40 cm H_2O, only one patient still showed atelectasis. Details for each patient are shown in figure 4; figure 5 shows the CT scans from one patient. The vital capacity anaesthetized (mean 4090 (850) ml) corresponded closely to the vital capacity awake, supine (mean 3940 (780) ml). This inflation to *P*aw = 40 cm H_2O may therefore also be called a vital capacity manoeuvre.

In order to obtain an estimate of the magnitude of the inflation necessary to diminish atelectasis, the airway pressure reducing the atelectatic area of scan 1 by 50% (= Paw_{50}) was determined. In the individual plots of airway pressure *vs* atelectatic area, a quadratic regression curve was fitted to the data (fig. 4). Paw_{50} was then estimated directly from the graph. The multiple linear regression between Paw_{50} and age, BMI and *C*rs showed the following relationship:

$$Paw_{50} = 29.9 - \text{age} \times 0.18 + \text{BMI} \times 0.94 - Crs \times 0.21$$

$$r = 0.973, \text{ analysis of variance: } P = 0.001$$

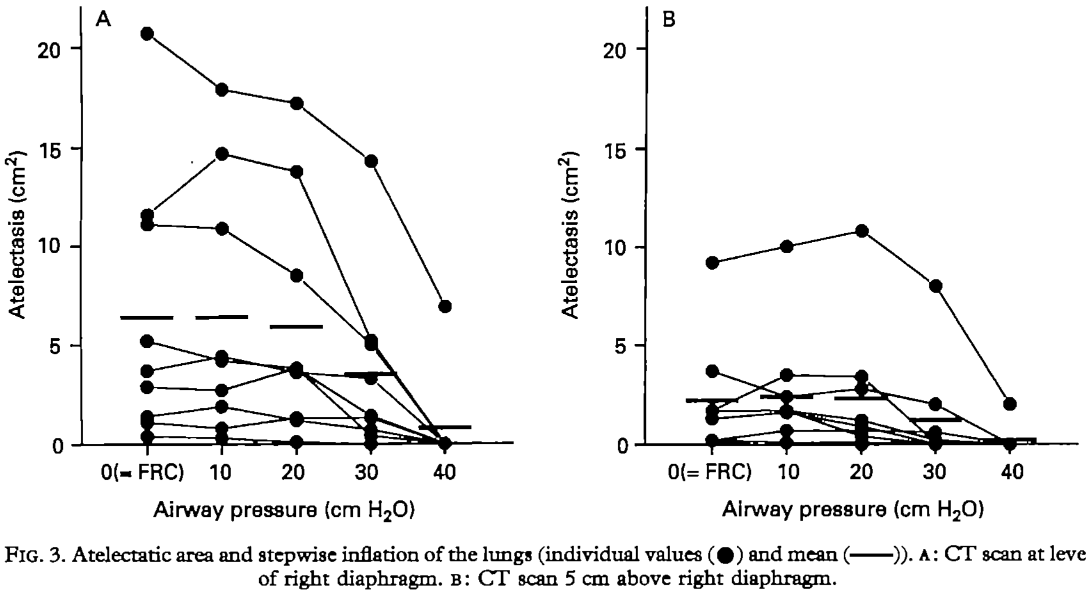

FIG. 3. Atelectatic area and stepwise inflation of the lungs (individual values (●) and mean (——)). A: CT scan at level of right diaphragm. B: CT scan 5 cm above right diaphragm.

TABLE III. *Atelectasis with stepwise inflation of the lungs (one patient excluded (no atelectasis at* Paw *= 0 cm H_2O))*

Airway pressure (cm H_2O)	Scan 1 atelectasis (cm^2)			Scan 2 atelectasis (cm^2)		
	Mean	Median	*P*	Mean	Median	*P*
0	6.4	3.7		2.2	1.7	
10	6.4	4.2	—	2.4	1.7	—
20	5.9	3.8	—	2.3	0.9	—
30	3.5	1.4	0.012	1.2	0.1	0.012
40	0.8	0.0	0.012	0.2	0.0	0.043

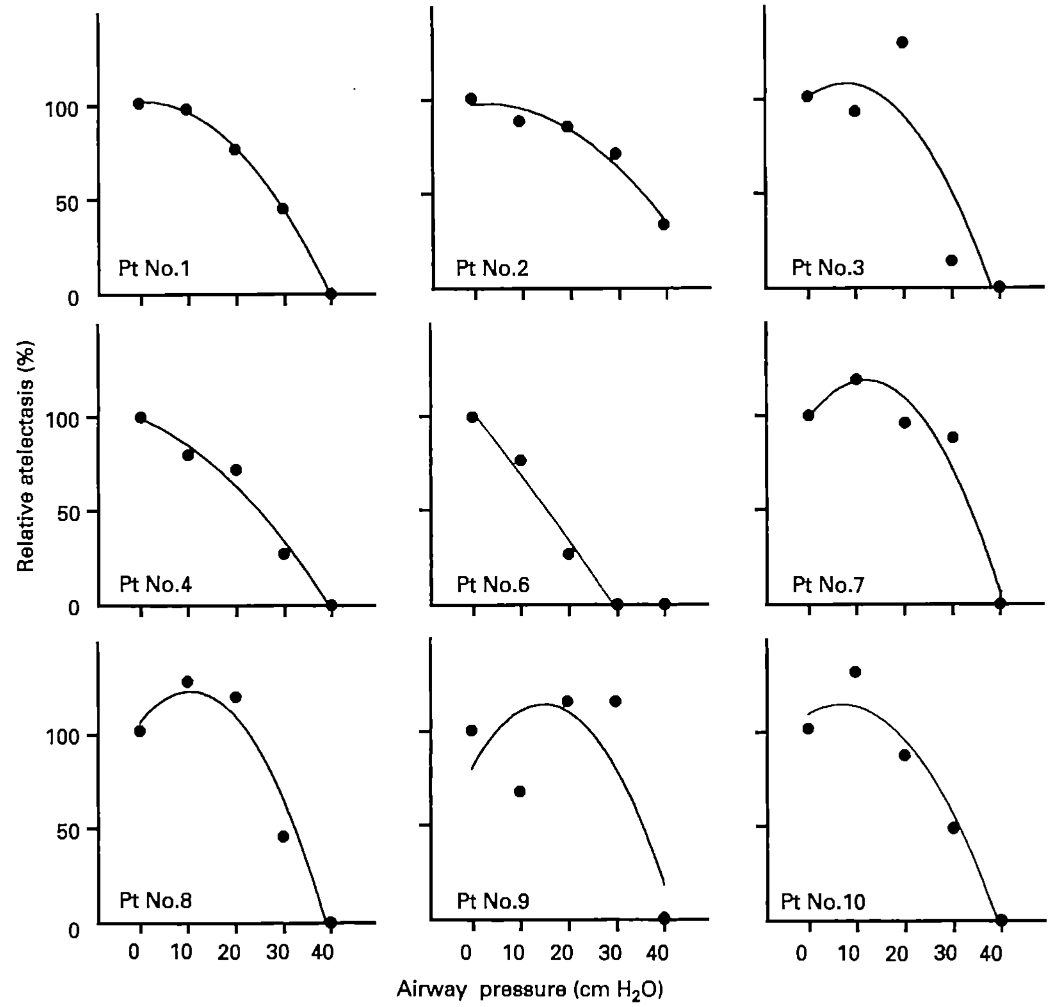

FIG. 4. Relative change in atelectatic area with stepwise inflation of the lungs for each individual patient, with a quadratic regression curve, calculated by the least squares method.

where age is in years; BMI = body mass index (kg m^{-2}); *C*rs = total compliance of the respiratory system (ml cm H_2O^{-1}).

During anaesthesia, the top of the left and right diaphragm was moved caudally between the position at *P*aw = 0 cm H_2O (functional residual capacity (FRC)) and *P*aw = 40 cm H_2O with means of 62 (14) mm and 70 (15) mm, respectively.

Repeated inflation (group 2)

With the first inflation to 30 cm H_2O, the amount of atelectasis was approximately halved (table IV, fig. 6). The second inflation resulted in an additional reduction of about 33%. With the third inflation to the same airway pressure, however, the further reduction in atelectasis was small (about 10%). The final inflation, to 40 cm H_2O (= vital capacity manoeuvre), eliminated the atelectasis.

With both recruitment manoeuvres, no clinically important adverse effects were observed.

DISCUSSION

The aim of this study was to estimate, in anaesthetized patients with healthy lungs, the degree of inflation of the lungs at which the amount of atelectasis may be reduced.

Computed tomography of the lung has become very helpful in analysing various aspects of lung pathophysiology, especially during anaesthesia [3] and in intensive care [12], and was therefore a

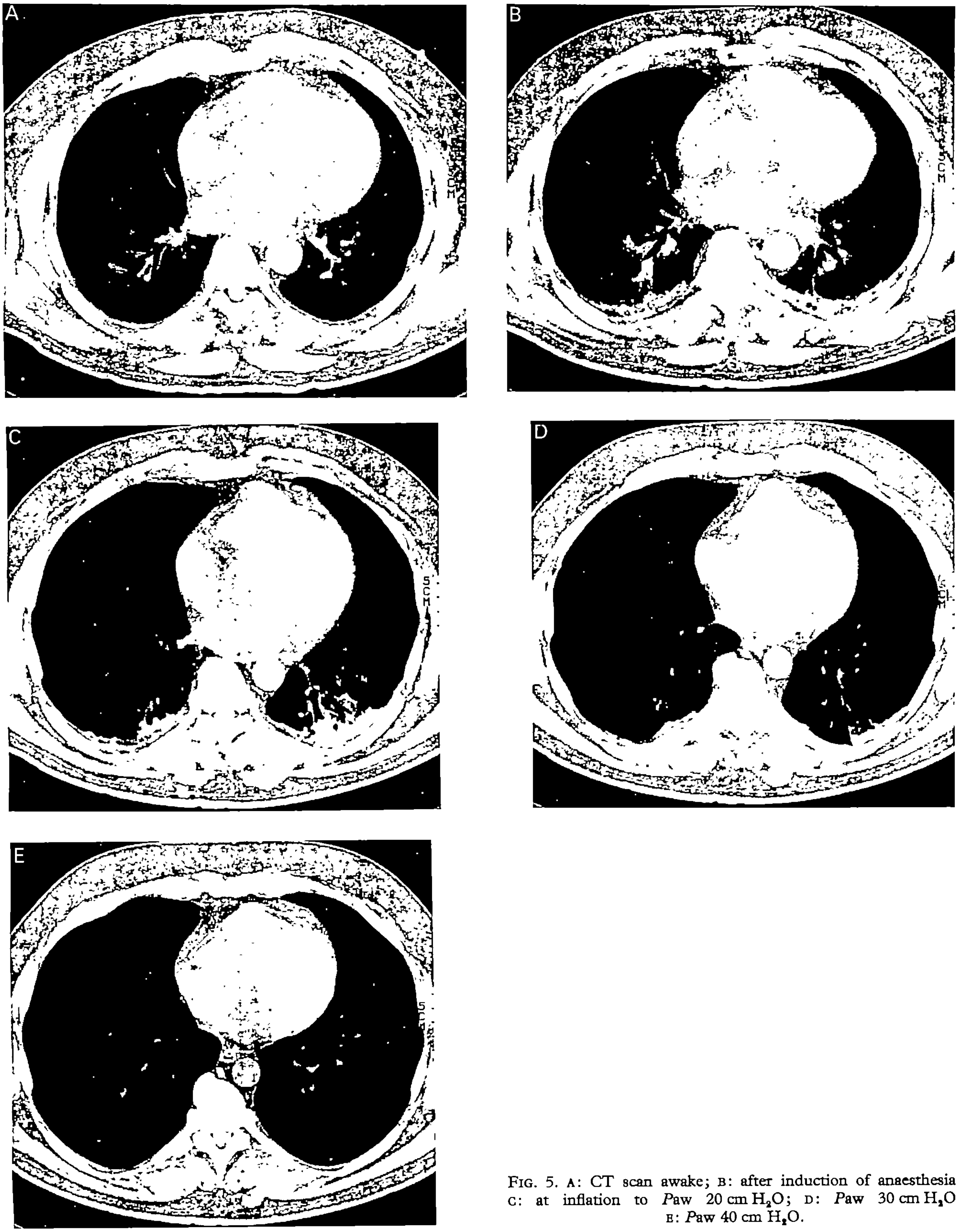

FIG. 5. A: CT scan awake; B: after induction of anaesthesia; C: at inflation to *P*aw 20 cm H_2O; D: *P*aw 30 cm H_2O; E: *P*aw 40 cm H_2O.

suitable technique to use in our study of atelectasis during inflation of the lung. However, it is well known that the atelectasis which appears after induction of anaesthesia is located mostly in dependent, basal parts of the lung of the supine patient [4]—a fact which was confirmed in our study, the caudal scans showing larger atelectasis than the cranial one. Thus positioning of the CT scan is critical to estimation of the amount of atelectasis: gradual cranial movement of the scan level may lead to a false conclusion of a reduction of atelectasis. In order to draw valid conclusions about changes in atelectasis, it is therefore important to visualize the same areas of lung tissue in subsequent scans. Our

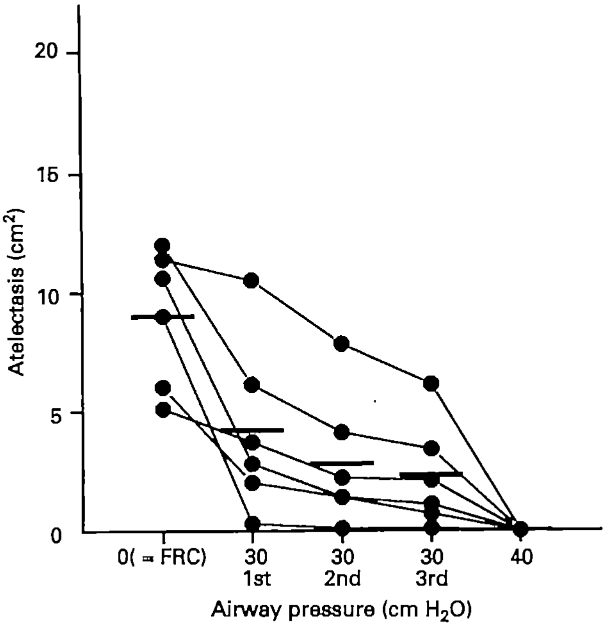

FIG. 6. Atelectatic area with repeated inflations of the lungs (individual values (●) and mean (——)).

TABLE IV. *Atelectasis with repeated inflations of the lungs*

Airway pressure (cm H_2O)	Atelectasis (cm^2)		
	Mean	Median	*P*
0	9.0	9.8	0.028
30 (1st)	4.2	3.2	0.028
30 (2nd)	2.8	1.8	0.043
30 (3rd)	2.2	1.6	0.028
40	0	0	

estimation of a movement of 15 mm with each increment of 10 cm H_2O was based on studies by Froese and Bryan [13] and Krayer and colleagues [14] and on our own observations. To avoid excessive exposure to x-rays and to avoid prolongation of inflation of the lung we decided to check the caudal movement of the diaphragm only at the end of the series of stepwise inflations in each patient. The measured distance between the position of the diaphragm at FRC and that at *P*aw 40 cm H_2O (about 66 mm) showed that our correction factor (giving a distance of 60 mm at 40 cm H_2O) was appropriate.

Anaesthesia

The results of our study are in accordance with earlier investigations in respect of atelectasis and shunt before and after induction of anaesthesia [5, 15]. We conclude, therefore, that our study population, although small, was similar to those investigated in earlier studies using the same techniques. An additional result of our study, the correlation between BMI and atelectasis, has not been described before, although a significant but weak correlation with another measure of body constitution, Broca's index, was shown by Strandberg and others [16]. In our study, the correlation was probably favoured by the rather large variability in body build, expressed as a wide range of BMI between the subjects, and by the fact that BMI may be a better reflection of body constitution than Broca's index [6]. This correlation fits well with the theory of compression atelectasis which states that the atelectasis in the dependent lung is mostly the result of cranial shift of the diaphragm in conjunction with a change in thoraco-abdominal configuration [3]. It is likely that this cranial shift is more marked in subjects with a heavier abdominal content.

Stepwise inflation

A marked reduction in atelectasis with stepwise inflation of the lungs occurred only at an airway pressure greater than 20 cm H_2O. Considering the average total compliance in patients in group 1 (75 ml cm H_2O^{-1}) an airway pressure of 20 cm H_2O results from approximately a doubling of the "conventional" tidal volume. This implies that a doubling of the tidal volume (often termed "sigh"), maintained for 15 s, does not significantly reduce either atelectasis or shunt. It has been known for many years that Pa_{O_2} may not necessarily be improved by a sigh [17].

However, as shown in this investigation, a vital capacity manoeuvre may open almost all atelectatic lung tissue and should therefore markedly diminish the amount of shunt. This interpretation of our data agrees with findings in an earlier study, in which the shunt in anaesthetized patients was reduced successfully with a "hyperinflation" (*P*aw = 40 cm H_2O, maintained for 40 s) of the lungs [18]. In the same investigation it was shown also that inflations to smaller pressures were not effective. Comparable findings were presented recently in a study of patients after open heart surgery [19]. Significant recruitment was found only at PEEP of 10–15 cm H_2O, resulting in end-inspiratory pressures of about 30 cm H_2O. It should be noted, however, that similar manoeuvres may be less successful in long standing atelectasis [20].

We tried to determine if there is a relationship between the amount of inflation necessary to reduce atelectasis and general parameters of the patient's constitution. For this purpose, the airway pressure required to reduce atelectasis by 50% was derived. An analysis of the multiple linear regression between Paw_{50} and BMI, age and *C*rs during anaesthesia was carried out. This relationship showed that the patients who needed a greater *P*aw to reduce atelectasis had a large BMI, were younger and had small *C*rs, but this must be interpreted cautiously because of possible time-dependent factors relating to the inflation manoeuvres, and the small number of patients in this study.

Repeated inflation

The first inflation to *P*aw 30 cm H_2O reduced atelectasis to the same extent as the inflation of the "stepwise manoeuvre" with the corresponding pressure. However, further inflations to the same airway pressure gradually showed a less marked effect. This is in agreement with the results of an earlier study [19], with no further change in the volume of recruited lung units and no change in static compliance of the respiratory system after the third increase in PEEP. This finding suggests that the critical opening pressure or the time constants are not equal in all units of a lung, even if those units are located in the same anatomical region—the dependent part of the lungs in our patients—or, expressed differently: in a given lung, not all alveoli may be opened by the same airway pressure.

It has yet to be established if the recruited lung tissue remains aerated over time and if this recruitment is accompanied by a similar decrease in or even disappearance of, pulmonary shunt and by a significant decrease in $(P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2})$.

Does the favourable effect of a vital capacity manoeuvre on atelectasis, as described in these findings, have a clinical application? Two possible adverse effects have to be borne in mind: barotrauma and disruption of the alveolo–capillary barrier. The possibility of barotrauma may not be excluded completely; however, it should be stressed that the amount of inflation we used was in accordance with the guidelines proposed by Leith [21]. It has been shown recently that in small animals periods of hyperinflation as short as 2 min may alter microvascular permeability, resulting in increased extravascular lung water [22]. Hyperinflation was defined in that study as ventilation to a preset peak airway pressure of 35 mm Hg (= 48 cm H_2O), corresponding to a tidal volume of 46 ml kg^{-1}. However, it is not known at which amount of inflation clinically significant alterations in lung tissue occur in human adults [23]. Furthermore, the vital capacity manoeuvre, as used in our study, results in a volume not larger than the awake, supine vital capacity. We therefore believe that such a manoeuvre still may be used in healthy adults having adequate clinical indication, such as significant hypoxaemia during general anaesthesia in an obese patient, in whom the development of atelectasis is likely, as shown above by the close relationship between body mass index and amount of atelectasis.

In summary, we found that atelectasis during general anaesthesia was not reduced by inflation of the lungs with a conventional tidal volume, or with a double tidal volume (sigh). With even larger inflation volumes, more than two repeated inflations to the same airway pressure added little to the recruitment of normal lung tissue. After an inflation to vital capacity, however, virtually all atelectatic lung tissue was re-expanded.

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FRESH GAS FLOW REQUIREMENTS DURING SPONTANEOUS VENTILATION: FRESH GAS FLOW TO TOTAL VENTILATION RATIO OR ML KG^{-1} MIN^{-1}?

N. SONI AND R. OOI

SUMMARY

Both the performance of breathing systems and recommendations for the fresh gas flows to be used in patients breathing spontaneously can be expressed in ml kg^{-1} min^{-1} or fresh gas:total ventilation ratio ($\dot{V}$F:$\dot{V}$E). We have examined the relationship between these two descriptions. The data of 106 subjects (awake volunteers and anaesthetized patients) were retrieved from the archives of previous work performed in our department. The two methods of describing the requisite fresh gas produced different results, with correlation coefficients (r) between the methods of r = 0.69 and r = 0.49 for the awake and anaesthetized groups, respectively. The results of the multiple regression models suggest that both baseline total ventilation and body weight may be used to predict the fresh gas flow requirements, but residual analysis did not discriminate which method was a better predictor. (Br. J. Anaesth. 1993; **71**: 796–799)

KEY WORDS

Equipment: breathing systems. Ventilation: fresh gas flow.

Considerable controversy has surrounded the issue of the fresh gas flow required to prevent rebreathing of carbon dioxide in anaesthetic breathing systems [1–8]. While the main controversy arises from the different criteria used for defining the onset of rebreathing [8, 9], interpretation of the literature is hampered by indiscriminate use of either the expression "ml kg^{-1} min^{-1}" or the fresh gas:total ventilation ratio ($\dot{V}$F:$\dot{V}$E) to describe the fresh gas flow. Indeed, these two means of expressing fresh gas flow have been used so indiscriminately as to imply that they may be interchangeable. However, neither the relationship between these two methods, nor the relative predictive capability of each has been examined.

We have therefore examined the relationship between fresh gas flow rate described in ml kg^{-1} min^{-1} and $\dot{V}$F:$\dot{V}$E, and compared both as predictors of that fresh gas flow which just produces rebreathing.

METHODS

Over the past few years, there have been several studies in our department which have examined the issue of rebreathing in both awake volunteers and anaesthetized patients [5, 8–12]. Data from these studies and our own unpublished data were retrieved from our archives (table I). In each study, the experimental method used with volunteers was that a predetermined fresh gas flow was reduced incrementally until the onset of rebreathing [13]. In anaesthetized patients, the fresh gas flow rate was set at the values at which rebreathing might be anticipated and only those patients in whom rebreathing was demonstrated were included in this survey [5]. The onset of rebreathing in these studies was defined either by the Kain and Nunn set of criteria [14] or by an increase in the minimum inspired carbon dioxide tension of 0.2 kPa [3]. In all studies, total ventilation ($\dot{V}$E) was measured during the control period where fresh gas inflow was set well in excess of the subject's predicted $\dot{V}$E. For the purpose of this study, the values of $\dot{V}$F:$\dot{V}$E and the corresponding fresh gas flow in ml kg^{-1} min^{-1} were noted at the onset of rebreathing for each subject, by each definition where applicable. The relationships between the corresponding pairs were then examined.

Statistical analyses were performed using the Statview 4.0 package (Abacus Concepts, California). The relationship between the two methods of expressing the requisite fresh gas flow at the onset of rebreathing was examined by correlation analysis. To determine which was the more consistent predictor of fresh gas flow requirements, a multiple regression technique was used, incorporating the variables: age, gender, awake or anaesthetized, criteria of rebreathing, type of Mapleson system, weight and baseline total ventilation. Further discrimination between the ability of weight and baseline ventilation to predict fresh gas flow was achieved by comparing the residuals of the model using body weight (M_W) with those from the model based on total ventilation (M_V). The interactions between the other variables (age, gender, rebreathing definition, awake/anaesthetized and weight or baseline total ventilation) were assessed separately by a cross-product simple linear interaction technique [15].

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TABLE I. *Sources of experimental data used in the study*

Reference	Number of subjects: Anaesthetized	Number of subjects: Awake	Type of system
[5]	24	—	Magill, Lack
[9]	—	9	Magill
[10]	—	9	Parallel Lack
[11]	7	6	Parallel Lack
[12]	—	8	Parallel Lack, Magill
[13]	10	20	Enclosed Magill, Magill
Unpublished data	—	13	Magill, enclosed Magill, Lack

RESULTS

Data from 65 conscious volunteers and 41 anaesthetized patients were analysed. The ASA categories in both groups were I/II. The age range was 18–39 yr and body weights 44–90 kg.

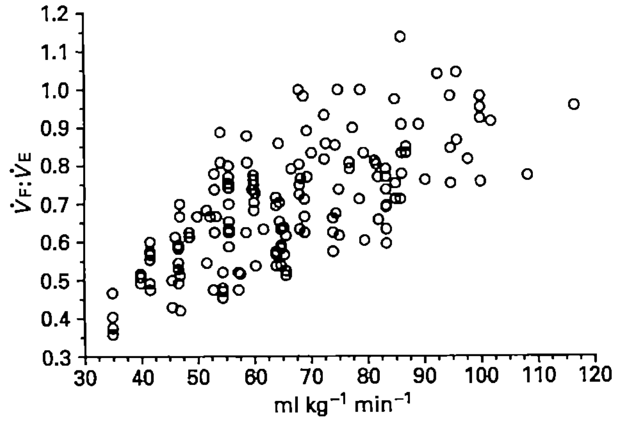

FIG. 1. Scatter plot of the relationship between the two methods of describing fresh gas flow requirements to prevent rebreathing (ml kg^{-1} min^{-1} and fresh gas flow: total ventilation ratio, $\dot{V}$F: $\dot{V}$E) for awake subjects.

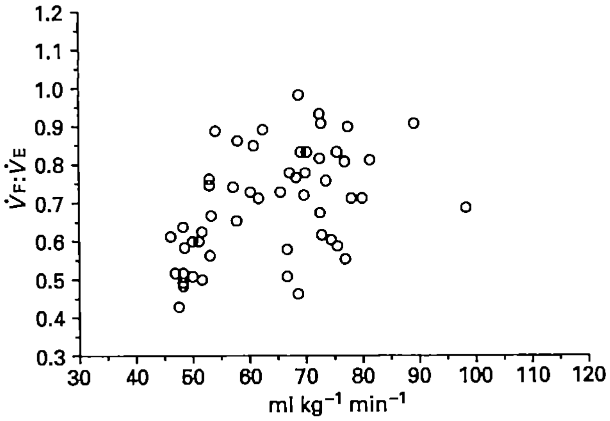

FIG. 2. Scatter plot of the relationship between the two methods of describing fresh gas flow requirements to prevent rebreathing (ml kg^{-1} min^{-1} and fresh gas flow: total ventilation ratio, $\dot{V}$F: $\dot{V}$E) for anaesthetized subjects.

The correlation coefficients (r) between the fresh gas flow values described by either ml kg^{-1} min^{-1} or $\dot{V}$F: $\dot{V}$E in the anaesthetized patients and the conscious volunteers were $r = 0.49$ and 0.69, respectively (figs 1, 2). Table II summarizes the values for the multiple regression models when body weight

TABLE II. *Summary of regression models for the awake and anaesthetized (anaesth.) subjects.* M_W = *Regression model incorporating body weight as a regressor;* M_V = *with baseline total ventilation as regressor;* r = *regression coefficient.* † *K&N = Kain and Nunn [14]; H = Humphrey [3]*

	M_W awake		M_V awake		M_W anaesth.		M_V anaesth.	
	r	P	r	P	r	P	r	P
Intercept	3.657	0.0006	1.859	0.0409	1.081	0.2791	2.652	0.0023
Age (yr)	−0.066	0.0043	−0.045	0.0211	−0.005	0.7898	−0.023	0.2821
Gender (1 = male; 0 = female)	−0.095	0.5373	−0.088	0.4592	−0.204	0.3625	−1.899	0.0637
Rebreathing (1 = K&N; 0 = H)†	1.154	0.5750	1.168	< 0.0001	0.400	0.1966	0.277	0.3802
Weight (kg)	0.018	0.0043	—	—	0.045	< 0.0001	—	—
Baseline total ventilation (litre min^{-1})	—	—	0.407	< 0.0001	—	—	0.323	0.0003
Magill (1 = Magill; 0 = other)	0.846	0.2792	0.825	0.2166	0.447	0.1879	0.591	0.145
Lack (1 = Lack; 0 = other)	0.761	0.3342	0.466	0.4865	—	—	—	—
Parallel								
Lack (1 = p. Lack; 0 = other)	0.764	0.3329	0.480	0.4743	0.220	0.4682	−0.135	0.6531
Enclosed Magill (1 = enc. Magill; 0 = other)	0.551	0.4834	0.462	0.4900	−0.220	0.4682	0.135	0.6531
r	0.668		0.770		0.694		0.671	
SD residuals	0.667		0.636		0.684		0.664	

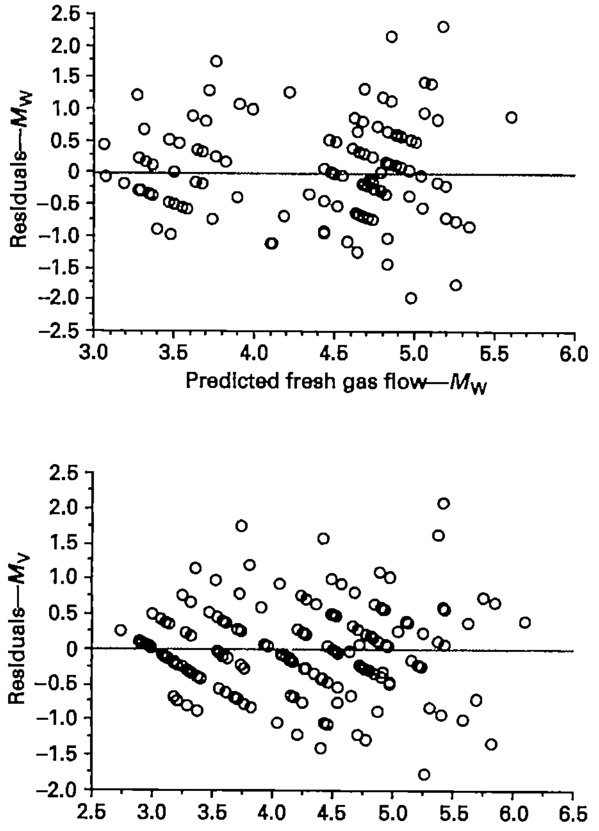

FIG. 3. Plot of residuals against predicted values from the regression models for awake subjects. M_W = Multiple regression model incorporating weight; M_V incorporates baseline total ventilation.

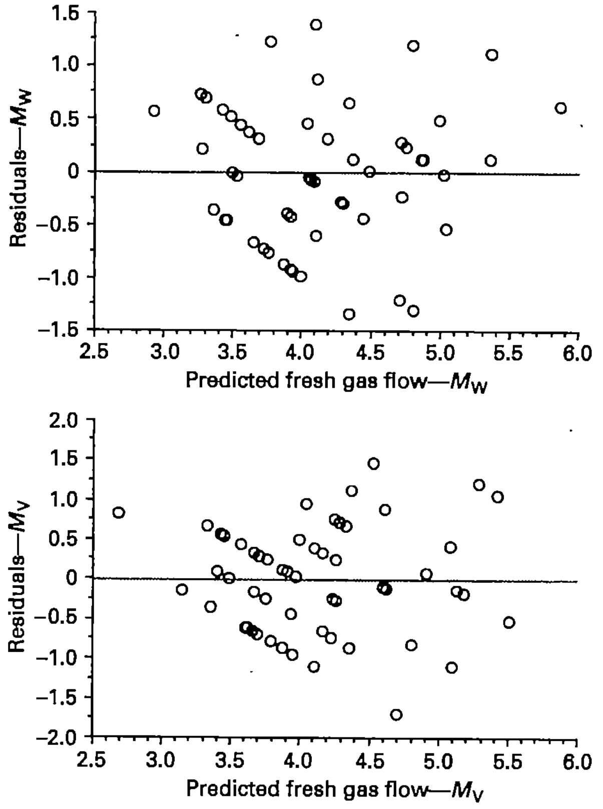

FIG. 4. Plot of residuals against predicted values from the regression models for anaesthetized subjects. M_W = Multiple regression model incorporating weight; M_V incorporates baseline total ventilation.

was used to determine fresh gas flow (M_W) and those when baseline total ventilation (M_V) was used. The plots of the residuals against predicted values from each of the models are shown in figures 3 and 4. For both groups, prediction of the fresh gas flow required to prevent rebreathing was influenced significantly ($P < 0.01$) by body weight and baseline total ventilation. The choice of rebreathing criteria also influenced prediction significantly in the awake subjects. There were no significant interactions ($P > 0.01$) between the dummy variables—age, gender, awake/anaesthetized, rebreathing criteria—and either weight or ventilation as predictors.

DISCUSSION

This retrospective study of the relationship between fresh gas flow expressed in ml kg^{-1} min^{-1} or $\dot{V}\text{F}:\dot{V}\text{E}$ ratio emphasizes the poor linear relationship between the two and it is clear that the predicted fresh gas flow requirement based on weight may be different from that using baseline total ventilation.

The use of $\dot{V}\text{F}:\dot{V}\text{E}$ has advantages, as it implies a physiological approach to rebreathing, but it has the disadvantage that total ventilation has to be measured and that the fresh gas flow rate has to be set before it is possible to measure the relevant ventilation. It is therefore not easily applied in clinical practice. In contrast, ml kg^{-1} min^{-1} is easily calculated and applied, as body weight is usually available. Despite its ease of application, the use of ml kg^{-1} min^{-1} has only recently been adopted—early studies described the fresh gas flow in terms of $\dot{V}\text{F}:\dot{V}\text{E}$. The use of ml kg^{-1} min^{-1} as a means of describing fresh gas requirements in spontaneous ventilation first appeared in the literature in 1978 [16–18], although it was already used commonly when describing flows for controlled ventilation. This convenient method of describing fresh gas flow rate, for spontaneous ventilation, rapidly became established, so that in the following decade many studies reported fresh gas flow in ml kg^{-1} min^{-1}.

Given the relationship between ml kg^{-1} min^{-1} and $\dot{V}\text{F}:\dot{V}\text{E}$, we attempted to determine which method is the more consistent predictor of fresh gas flow. The results of the multiple regression model analyses demonstrate that the requisite fresh gas flow was influenced significantly by both weight and baseline total ventilation, but did not discriminate between the two. To evaluate this, residual analysis was performed on each of the regression models. The finding of similar SD values for each of the models—ranging from 0.636 to 0.684—suggests that both body weight and baseline total ventilation are comparable as predictors. The residual SD of about 0.7 litre min^{-1} implies that, regardless of whether weight or baseline ventilation is used, and even when taking account of the significant effects of gender and rebreathing criteria, in 5 % of patients the predicted value may be in error by more than about 1.5 litre min^{-1}—that is, the 95 % prediction interval falls within twice the SD [19].

In this study, the data from the anaesthetized and awake groups were not pooled together, as the experimental methods for determining the requisite fresh gas flow were different, particularly as the studies in the anaesthetized group involved greater steps in fresh gas flow reduction. The different experimental methods also explain the finding of non-significant effects of the rebreathing criteria in anaesthetized subjects—only one value for rebreathing was obtained from each patient.

In conclusion, these two methods of describing the fresh gas flow cannot be converted directly one to the other. While both may be reliable methods for describing the fresh gas flow, the ease of using the body weight favours its clinical use. Both are obviously valid methods and a sensible compromise would be to report both when comparing the performance of breathing system.

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British Journal of Anaesthesia 1993; 71: 800–802

EFFECT OF CRICOID PRESSURE ON EASE OF INSERTION OF THE LARYNGEAL MASK AIRWAY

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SUMMARY

We have evaluated the effects of cricoid pressure on laryngeal mask airway (LMA) insertion after an elective rapid sequence induction in 100 patients allocated randomly to two groups. An attempt was made to insert the LMA after application of cricoid pressure in one group and with no pressure in the other. The anaesthetist was blinded to the application of cricoid pressure. Insertion was successful in 45 of 50 patients in the cricoid pressure group and in 49 of 50 patients in the non-cricoid group ($P < 0.1$*) We discuss the implications of these findings for failed intubation in the non-fasted patient.* (Br. J. Anaesth. 1993; **71**: 800–802)

KEY WORDS

Airway: cricoid pressure. Equipment: laryngeal mask airway. Complications: regurgitation.

The laryngeal mask airway (LMA) may be used in the case of failed conventional intubation, as it can be used as an alternative airway or as an aid to intubation [1]. It can rapidly provide a clear and unobstructed airway in 94–98% of patients [2], but there is no protection against regurgitated gastric contents. The objective of airway management in failed intubation is "oxygenation without aspiration" [3] and maintaining cricoid pressure is considered critical in preventing this complication [4]. When positioned ideally, the tip of the LMA cuff lies behind and above the cricoid cartilage. The application of cricoid pressure may therefore reduce the ease of insertion of the LMA. The presence of a correctly placed LMA may also theoretically interfere with the effectiveness of cricoid pressure. However, a recent postmortem study demonstrated that the presence of the LMA does not compromise cricoid pressure [5].

The LMA has been used successfully in cases of failed intubation in non-fasted patients [6–10]. In three of these reports, cricoid pressure was maintained during and after LMA insertion [7–9] and in one report cricoid pressure was eased before insertion of the LMA and then reapplied [10]. No specific problems were noted with LMA insertion. However, Christian, McClune and Moore reported functional failure of the LMA after insertion with cricoid pressure applied [11]. The 1985–1987 *Report on Confidential Enquiries into Maternal Deaths in England and Wales* recommended that cricoid pressure be maintained during insertion of the LMA in the event of failed intubation [12]. An unblinded clinical study confirmed this recommendation [13], but a recent single-blinded study found that the LMA could not be inserted in the majority of patients with cricoid pressure applied [14].

The following randomized, single-blinded study was designed to assess further LMA insertion with cricoid pressure applied in circumstances which more closely represent an unanticipated failed intubation.

PATIENTS AND METHODS

After obtaining Ethics Committee approval and informed written consent, we studied 100 ASA I and II patients aged 18–80 yr undergoing elective superficial or extremity surgery. Patients were excluded if they had a history of previous upper abdominal surgery, hiatus hernia, oesophageal reflux, peptic ulceration, morbid obesity or were otherwise considered at risk of aspiration. The modified Mallampati classification was noted [15, 16].

The ECG and oxygen saturation were monitored continuously and arterial pressure was measured non-invasively. After 3 min of preoxygenation, anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and, after loss of consciousness, suxamethonium 1 mg kg^{-1} was administered. No attempt was made to inflate the patient's lungs via a face mask. Patients were allocated randomly to have either cricoid pressure or pseudo-cricoid pressure applied by a trained technician before loss of consciousness. Adequate time was given before induction for the cricoid cartilage to be identified. Cricoid pressure involved application of single-handed cricoid pressure as described originally by Sellick [4]. Pseudo-cricoid pressure involved touching the cricoid cartilage, but not applying pressure. The anaesthetist was blinded to the application of cricoid pressure by a drape placed over the neck of the patient and arm of the technician. The drape allowed full visual assessment of thoraco-abdominal movement. Direct laryngoscopy was performed by the anaesthetist and the view of the cords scored [17]. This did not unblind the anaesthetist. A prepared LMA was then

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inserted using the standard approach with the cuff fully deflated (No. 3 for women and No. 4 for men) [18]. When in position, the cuff was inflated fully (25 ml No. 3, 35 ml No. 4). The time taken from removal of the laryngoscope to inflation of the LMA cuff was noted. A fibreoptic scope was passed to the level of the mask aperture bars to score the position of the LMA as follows [19]: 4 = only cords seen; 3 = cords plus posterior epiglottis seen; 2 = cords plus anterior epiglottis seen; 1 = cords not seen, but subsequent function adequate; 0 = failure—failure to insert into the hypopharynx within 1 min, a reduction in Sp_{O_2} to less than 95% or failure to function where the cords were not seen fibreoptically. Function was assessed by gentle hand ventilation and synchronized expansion of the chest. Function was judged adequate only if chest expansion was grossly obvious. When the score had been determined, cricoid or pseudo-cricoid pressure was released and anaesthesia proceeded normally. Fibreoptic scoring and functional assessment were performed by the anaesthetist who inserted the LMA.

The study was conducted by three senior registrars experienced in the elective use of the LMA (at least 400 LMA insertions). Six trained technicians assisted with the study. All had been certified as competent at applying cricoid pressure and were observed correctly applying cricoid pressure by the authors before the study began.

Data were analysed statistically with chi-square. Significance was taken as $P < 0.05$.

TABLE I. *Patient data for cricoid pressure and pseudo-cricoid pressure groups (number or mean* (SD) *[range])*

	Cricoid pressure	Pseudo-cricoid pressure
Sex (M:F)	40:10	37:13
Age (yr)	39 [18–80]	37 [18–79]
Weight (kg)	76 (15) [49–113]	78 (17) [45–120]

TABLE II. *Distribution of Mallampati [15, 16] and laryngoscopic (laryng.) scoring [19] for cricoid and pseudo-cricoid groups (number)*

	Cricoid pressure		Pseudo-cricoid pressure	
Score	Mallampati	Laryng.	Mallampati	Laryng.
1	20	25	27	24
2	19	18	17	19
3	10	6	6	6
4	1	1	0	1

TABLE III. *Results of fibreoptic scoring. Score 4 = only cords; 3 = cords plus posterior epiglottis; 2 = cords plus anterior epiglottis; 1 = cords not seen, but function adequate; 0 = failure to insert or to function. No significant differences between groups (P < 0.1, chi-square)*

	Score					Median score
	4	3	2	1	0	
Cricoid	14	6	13	12	5	2.24
Pseudo-cricoid	26	6	10	7	1	2.98
Total	40	12	23	19	6	2.61

RESULTS

We studied 77 men and 23 women (mean (range) age and weight 38 (19–80) yr and 77 (45–120) kg, respectively) (table I). The median Mallampati score was 1.71 (range 1–3) and the median score at direct laryngoscopy was 1.6 (range 1–4) (table II). Patient data and the distribution of Mallampati classification and laryngoscopic scoring were similar for both groups.

The mean (SD) time for successful LMA insertion in the pseudo-cricoid group was 9 (3) s (range 5–18 s); that in the cricoid pressure group was 10 (5) s (range 5–35 s). All fibreoptic scoring was made within 20 s of LMA insertion. The overall successful insertion rate was 94% (90% (45/50) in the cricoid group and 98% (49/50) in the pseudo-cricoid group). The distributions by fibreoptic scoring of both groups were compared using chi-square. The median score for the pseudo-cricoid group was greater than that for the cricoid group (2.98 *vs* 2.24), but this was not statistically significant (table III). There was no correlation between Mallampati classification or laryngoscopic score and fibreoptic score. Five fibreoptic scores of 0 occurred in the cricoid pressure group and one score of 0 occurred in the pseudo-cricoid group. Failures were not associated with any particular anaesthetist or technician. In the cricoid group, one failure occurred when the LMA could not be passed into the hypopharynx; the remaining four failures were the result of inadequate positioning in the hypopharynx and poor function. In these four patients, the LMA was reinserted without cricoid pressure when spontaneous ventilation anaesthesia recommenced and three scores of 2 and one score of 1 were achieved, suggesting that cricoid pressure had prevented insertion. Failure to pass the LMA into the hypopharynx within 1 min was the cause of the single failure in the pseudo-cricoid group. A later attempt produced a score of 2. The range of Mallampati and laryngoscopic scores in the failure group was 1–2 and was similar to those associated with successful insertion.

DISCUSSION

Two previous studies have assessed the effect of cricoid pressure on LMA insertion [13, 14]. An unblinded consecutive study of 80 patients demonstrated that application of single-handed cricoid pressure did not significantly reduce ease of insertion with the cuff partially inflated (success rate 34/40 *vs* 37/40) [13]. These findings were in marked contrast to a more recent single-blinded, controlled study of 42 patients conducted by Ansermino and Blogg, in which LMA insertion was successful in only three of 20 patients with double-handed cricoid pressure [14]. Their recommendations were that cricoid pressure should be released transiently before LMA insertion, despite the presence of a full stomach. It is important to attempt to resolve this controversy so that firm guidelines may be made for the role of the LMA in a failed intubation drill. A larger study was required, therefore, which more closely simulated the sequence of events occurring during a failed intubation in the patient with a full stomach.

Any attempt at prospectively duplicating the precise circumstances of failed intubation would be either ethically unacceptable or logistically difficult to perform. To simulate pharyngeal trauma and bleeding caused by multiple attempts at laryngoscopy and intubation, progressive hypoxia and a sense of panic in the anaesthetist and assistants is not possible for trial purposes. Furthermore, failed intubation is more common for junior anaesthetists and attempts at LMA insertion may occur when conditions are suboptimal. It is also difficult to provide controlled amounts of cricoid pressure in a clinical setting. In both previous studies and the present study, the LMA was inserted in a controlled situation by experienced operators when conditions for LMA insertion were favourable, and in this respect may not reflect the clinical situation.

The current single-blinded study represents an improvement on the first two studies because it simulated more closely the circumstances of failed intubation and involved three operators, a larger number of patients and more objective criteria for determining successful placement of the LMA. Preoxygenation, thiopentone, the application of cricoid pressure before loss of consciousness, suxamethonium, laryngoscopy and intubation is the usual sequence of events during rapid sequence induction, and was followed in this study. The criteria used to assess successful insertion of the LMA were fibreoptic positioning and function. In all patients with a score of 2 or greater, the vocal cords could be seen clearly, which would indicate that IPPV was possible, and this was confirmed by assessment of function. Patients in whom the cords could not be viewed required functional assessment to differentiate between scores of 1 or 0. This current study did not assess if cricoid pressure interfered with LMA function when spontaneous ventilation had resumed. In a previous study conducted by one of the authors, cricoid pressure was applied to 80 spontaneously breathing patients when the LMA was *in situ* [13]. This caused the laryngeal inlet to tilt anteriorly by 10–40°, but did not interfere with LMA function. There is also no evidence that neuromuscular block interferes with LMA insertion [20]. It may be suggested that data about LMA insertion taken from patients with normal airways cannot be extrapolated to those who present difficulty in intubating. However, data from this study and a previous study by Mahiou and colleagues, of 362 patients, indicate that there is no correlation between ease of insertion of the LMA and either Mallampati or Cormack and Lehane scoring [21]. This suggests that ease of insertion is similar for both the normal and abnormal airway and implies that our findings are relevant to the patient whose trachea cannot be intubated.

The results of this current study suggest that, although cricoid pressure reduces the ease of insertion of the LMA by 8 %, successful insertion can still be achieved in 90 % of patients within an average of 10 s in experienced hands. The degree to which these findings may be extrapolated to the clinical management of failed intubation in the non-fasted patient is open to question. We would suggest that, when the use of the LMA is considered appropriate, insertion should be attempted initially with maintained cricoid pressure and, if this fails, a second attempt should be made with transient release of cricoid pressure. We would also suggest that, where possible, LMA insertion should be attempted before the effects of neuromuscular block or the induction agent have terminated.

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RADIOLOGICAL EXAMINATION OF THE INTRATHECAL POSITION OF MICROCATHETERS IN CONTINUOUS SPINAL ANAESTHESIA

T. STANDL AND H. BECK

SUMMARY

*There have been few studies of the intrathecal position of spinal catheters in continuous spinal anaesthesia. This prospective study was designed to examine radiologically the intrathecal position of 28-gauge spinal catheters. We studied the entry into the subarachnoid space and the intrathecal position of 68 spinal catheters. In 50%, the catheters passed in a cranial direction, in 34% the catheters remained at the level of the puncture site and in 16% the catheters were directed caudally. The intrathecal position of the catheters did not depend on the level of the lumbar puncture (*P = *0.6246), but was dependent on the position of the patient during insertion of the catheter (*P = *0.0093), and on the depth of insertion (*P = *0.0099). Our study suggests that patients should be in a sitting position during insertion of a subarachnoid microcatheter and that the depth of insertion should not exceed 4 cm.* (Br. J. Anaesth. 1993; **71**: 803–806)

KEY WORDS

Anaesthetic techniques: subarachnoid.

Tuohy, in 1944, was the first to describe the technique of continuous spinal anaesthesia using a 15-gauge needle and a urethral catheter placed into the subarachnoid space [1, 2]. In 1947, Courbelo modified Tuohy's technique and inserted a urethral catheter into the extradural space [3]. Since that time, continuous extradural anaesthesia has become more popular than continuous spinal anaesthesia because of its smaller incidence of postdural puncture headache [4]. However, with the availability of spinal microcatheters, continuous spinal anaesthesia is enjoying a renaissance [5–9]. There are several studies on the position of extradural catheters during continuous extradural anaesthesia [10–13], but only a few studies have investigated the position of large-gauge spinal catheters [11, 14]. Recent publications suggest that the intrathecal position of spinal catheters affects the clinical outcome of continuous spinal anaesthesia [15, 16]. The present prospective study was designed to investigate the intrathecal position of spinal catheters using conventional radiography.

PATIENTS AND METHODS

We studied 68 patients who received continuous spinal anaesthesia for elective orthopaedic operations on the lower extremities (table I). None of the patients had abnormality of the vertebral column or vertebral surgery before the study. The study was approved by the hospital's Ethics Committee and informed consent was obtained from all patients. After oral premedication with midazolam 7.5 mg 1 h before anaesthesia, the patients were allocated randomly to two groups: in group A (32 patients), lumbar puncture and intrathecal insertion of the catheter were performed with the patient in the sitting position; in group B (36 patients), the lumbar puncture and intrathecal insertion of the catheter were performed with the patient in the right lateral position. In all patients, a 22-gauge Quincke needle was inserted at an angle of 45° through the anaesthetized skin using the midline approach at the L2–3, L3–4 or L4–5 interspace. When piercing the dura, the needle bevel was directed parallel to the dural fibres [17]. After aspiration of clear CSF, the needle was turned cephalad in order to direct the catheter into a cranial position. A 28-gauge spinal catheter (Cospan Kendall, Mansfield, Mass.) was inserted 2 cm (minimum) to 5 cm (maximum) into the subarachnoid space by the same anaesthetists. After removal of the needle, the stylet was withdrawn from the catheter and the catheter was secured in the

TABLE I. *Characteristics and classification of 68 patients allocated randomly to group A (sitting) and group B (right lateral) (number or mean (SD) [range])*

Characteristic	Group A	Group B
No. patients	32	36
Sex (M:F)	16:16	18:18
Age (yr)	63 [23–83]	61 [26–84]
Weight (kg)	72 (2) [54–95]	75 (2) [49–93]
Height (cm)	166 (1) [150–181]	170 (2) [150–188]
Interspace		
L2–3	4	5
L3–4	21	24
L4–5	7	7
Insertion depth (cm)		
2.0–3.0	10	11
3.1–4.0	15	19
4.1–5.0	7	6

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form of a loop at the level of the puncture site. The catheter level at the patient's skin was marked and a tape fixed on the patient's back before the patient was placed in a horizontal position. Then plain 0.5 % bupivacaine 2.5 ml was injected into the catheter. If required, additional doses of 0.5 % bupivacaine were injected to produce an analgesic level of T10. After completion of surgery, the catheter remained *in situ* for postoperative pain relief.

On the first day after operation, the position of the catheter was compared with the preoperative level. For radiological control of the intrathecal position of the catheter, a dose of Iopamidol 1 ml (= 200 mg of iodine) (Solutrast 200 M, Byk Gulden, FRG) was injected into the catheter to increase the contrast of the intrathecal part of the catheter and a conventional antero-posterior x-ray of the lumbar spine was performed. Entry of the spinal catheter into the subarachnoid space and the intrathecal position of the catheter were evaluated as "cranial" (tip of the catheter above the lower edge of the cranial lumbar vertebral body), "caudal" (tip of the catheter below the upper edge of the caudal lumbar vertebral body) or "at the level of the puncture site" (tip of the catheter between lower edge of the cranial and upper edge of the caudal lumbar vertebral body). The results were assessed by Freemann–Halton test [18].

The intrathecal position of the microcatheter was tested statistically in respect of the point of entrance of the catheter into the subarachnoid space (lumbar interspace), the position of the patient during insertion of the catheter (sitting or right lateral) and intrathecal advancement of the catheter (insertion depth). Results were considered significant at $P < 0.01$.

RESULTS

Adequate analgesia was produced in all 68 patients and there was no significant difference between the two groups of patients. In all patients, there was no change of the marked catheter level at the skin on the first day after operation compared with the level noted immediately after catheter insertion.

Radiological evaluation of the intrathecal position of the spinal catheters revealed nine catheters penetrating the dura at the L2–3 interspace, 45 catheters penetrating the dura at L3–4 and 14 catheters penetrating it at L4–5. Thirty-four spinal catheters were in a cranial position, 11 catheters were in a caudal position and 23 catheters remained at the level of the puncture site.

The intrathecal position of the 68 spinal catheters in relation to the interspace at which the catheters were threaded into the subarachnoid space is shown in table II. There was no statistically significant dependence of the intrathecal position of the catheters on the lumbar interspace at which catheter insertion had been performed ($P = 0.63$).

The intrathecal position of the 68 spinal catheters in relation to the position of the patients during insertion of the catheters into the subarachnoid space was significantly different between the groups (table II). In group A (sitting patients), 69 % of the catheters were directed cephalad, while in group B (patients in right lateral position) only 33 % of the catheters were cephalad. In group A, 6 % of the catheters and in group B 25 % of the catheters were directed caudally. There was a greater number of catheters at the level of the puncture site in group B (42 %) than in group A (25 %). The differences between groups A and B in intrathecal positions of the spinal catheters were statistically significant ($P = 0.0093$).

The intrathecal position of the 68 spinal catheters in relation to the intrathecal depth of insertion of the catheters also revealed significant differences between all three insertion depths. Spinal catheters inserted more than 4 cm were more caudal (31 %), while those inserted 2–3 cm or 3.1–4 cm had fewer caudal positions (10 % and 15 %). The majority of catheters inserted only 2–3 cm remained at the level of the puncture site (62 %). The number of catheters that remained at the level of the puncture site decreased with increasing depth of insertion (table II). The differences in intrathecal positions of the spinal catheters between the three different intrathecal insertion depths were significant ($P = 0.0099$).

TABLE II. *Intrathecal position of 68 microspinal catheters dependent on interspace of lumbar puncture, patient's position during catheter insertion and intrathecal insertion depth*

	Intrathecal position		
	Cranial	Puncture site	Caudal
Interspace			
L2–3	3 (33 %)	3 (33 %)	3 (33 %)
L3–4	24 (53 %)	15 (33 %)	6 (13 %)
L4–5	7 (50 %)	5 (36 %)	2 (14 %)
Patient's position			
Sitting (group A)	22 (69 %)	8 (25 %)	2 (6 %)
Right lateral (group B)	12 (33 %)	15 (42 %)	9 (25 %)
Insertion depth (cm)			
2.0–3.0	6 (28 %)	13 (62 %)	2 (10 %)
3.1–4.0	20 (59 %)	9 (26 %)	5 (15 %)
> 4	8 (61 %)	1 (8 %)	4 (31 %)

DISCUSSION

Most anaesthetists intend to introduce extradural or spinal catheters in a cranial direction [11]. Correct position of the catheter tip at the intended level may reduce the required dose of local anaesthetics needed for block of a specific area. Therefore, special needle shapes (such as Tuohy's needle) have been designed to guide the catheters towards an intended direction within the extradural or subarachnoid space [4]. Several studies have investigated the position of extradural catheters within the vertebral column [10–13]. However, few investigations deal with the intrathecal position of spinal catheters [11, 14]. Bridenbaugh and colleagues [11] observed that 56–69 % of catheters placed into the subarachnoid space were passed cranially, but they gave no information on the type of the catheter used. Van Gessel, Forster and Gamulin [14] observed that all of 30 spinal catheters (20-gauge) inserted 3–4 cm into the subarachnoid space were directed cranially. In contrast, studies on the position of extradural catheters have shown that a cranial direction occurs only in 14–65 % [10–13]. Because of anatomical differences between the extradural and subarachnoid space, we expected a greater number of cranially directed spinal catheters in our study. However, our results with the 28-gauge spinal catheters are consistent with previous results obtained with extradural catheters [10–13]. The difference between our data and those of van Gessel's group [14] suggests that the rigidity of the larger-bore 20-gauge spinal catheters may allow better control of the direction of spinal catheters. However, the risk of secondary perforation of the dura, neurological damage or postdural puncture headache is greater for spinal catheters with larger diameters [7, 19–22].

In the study by van Gessel, Forster and Gamulin [14], the patients were examined at the end of the operation. In the present study, the patients were examined on the first day after operation. There was no change in the position of the marked catheters at the skin, but we cannot exclude totally changes in the intrathecal position of the catheters during this period of 24 h. However, because of strict immobilization of all patients, it is unlikely that the catheters changed their intrathecal position.

The shape of the needle and the design of the tip may help to guide the catheter into the intended intrathecal direction. In the present study, we used a needle with a Quincke tip. This produced unpredictable intrathecal positions of the catheters. It is possible that needles with a special tip or a ramped opening on their side (Whitacre or Sprotte needle [23, 24]) may facilitate achievement of the intended direction of a spinal microcatheter.

In contrast with our intention to direct all 68 spinal catheters cranially, only 50 % of the catheters passed cephalad, 34 % of the catheters remained at the level of the puncture site and 16 % were passed caudally. These results are consistent with the findings of Swayze and Skerman [25], who used the same spinal catheters in a spinal canal model.

The clinical consequences of the different intrathecal catheter positions have not been investigated systematically. There may be a greater risk of neurological sequelae associated with the use of caudally directed spinal microcatheters in combination with large doses of hyperbaric local anaesthetics in continuous spinal anaesthesia. Rigler and Drasner [15] demonstrated in a model of the subarachnoid space, that this combination resulted in maldistribution and a large local concentration of local anaesthetic. Maldistribution of local anaesthetic with caudally directed spinal catheters may also explain the restricted sacral block described by Chan and Smyth [16] or neurological damage (cauda equina syndrome) observed by Lambert and Hurley [26] and Rigler and colleagues [27]. Therefore, cranial direction of the spinal catheter or a position at the level of the puncture site may be associated with a smaller incidence of complications.

Our study showed that the level of the lumbar interspace selected for insertion of the spinal catheter had no effect on the intrathecal catheter position. In contrast, our data suggest a greater rate of cranially directed catheters in patients who were sitting during insertion of the catheter. It is possible that the sitting position increases the lumbar subarachnoid space (because of increased hydrostatic pressure). This may reduce the incidence of contact between the dura on the opposite side or with intrathecal spinal nerves. This contact may help to guide the intrathecal direction of a spinal catheter [28]. In contrast with our findings, Swayze and Skerman [25] obtained a greater number of catheters directed cephalad and no caudally directed catheter in their model simulating the right lateral decubitus position compared with the model simulating the sitting position. The present study also showed that catheters inserted deeper are more likely to be directed cranially or caudally. Thus an insertion depth of 2–4 cm seems to be the optimum and is consistent with the results of Swayze and Skerman [25]. Mollmann and colleagues [28] found that malposition of spinal catheters could be avoided by inserting the catheters only 2 cm into the subarachnoid space. Catheters inserted more than 3 cm can also produce intrathecal loops or coils and this may lead to inadequate block or even neurological damage [16, 26, 27].

The intrathecal position of spinal catheters is certainly not the only factor influencing the clinical outcome of continuous spinal anaesthesia. Other variables such as size of the spinal catheter and injection rate may also influence the effect of a local anaesthetic in continuous spinal anaesthesia [15]. The characteristics of the local anaesthetic used, such as baricity and concentration, are important [29]. Most of the reports of neurological problems after continuous spinal anaesthesia describe patients in whom hyperbaric 5 % lignocaine was used [16, 26, 27].

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EFFECT OF LATE POSTURE CHANGE ON THE LEVEL OF SPINAL ANAESTHESIA WITH PLAIN BUPIVACAINE

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SUMMARY

*We studied 40 patients, 18–60 yr, undergoing orthopaedic surgery of the lower limb under spinal anaesthesia. A midline lumbar puncture was performed in the L3–4 interspace using a 27-gauge needle with the patient in the lateral horizontal position. Plain bupivacaine 3 ml at room temperature was injected. The cephalad level of analgesia was assessed by pinprick 60 min after injection of local anaesthetic, at the end of surgery and again after the patient was moved into bed. All patients had a segmental level of the block of L1–T5 at the beginning of the study. The upper half of the patient's body was then tilted to a 30° head-up position. Segmental spread was subsequently assessed by pinprick at 5-min intervals for 30 min. In six of the 40 patients (15%), increased cephalad spread of spinal analgesia occurred. The mean time from induction of spinal anaesthesia was shorter in these six patients (mean 92 min, range 80–115 min) than in the patients whose block did not change or was decreasing during the 30-min test (mean 119 min, range 83–210 min) (*P < 0.05*). We conclude that the patient should remain in the supine horizontal position until recovery from the spinal block.* (Br. J. Anaesth. 1993; **71**: 807–809)

KEY WORDS

Anaesthetic techniques: spinal. Pharmacology: bupivacaine.

It is thought that the distribution of local anaesthetic solution in the cerebrospinal fluid is complete within 15–20 min [1–3]. However, after subarachnoid administration of hyperbaric 0.5% bupivacaine [4, 5] and other hyperbaric local anaesthetic solutions [4], the spread of the block has been shown to change further 45–60 min later, when the patients were moved to another position. With plain 0.5% bupivacaine, the cephalad spread of spinal block occasionally continues beyond 60 min [6–11].

We have observed recently two patients who had severe transient bradycardia and hypotension after re-positioning 80 and 125 min after subarachnoid injection of local anaesthetic. In both patients, the level of spinal anaesthesia was noticed to have increased by four to five segments (to T1 and to T6, respectively) compared with the levels at 60 min. We have therefore studied the effect of a 30° head-up tilt position on the level of spinal anaesthesia in the immediate postoperative period—that is, more than 60 min after the subarachnoid injection of plain 0.5% bupivacaine.

PATIENTS AND METHODS

We studied 40 ASA I–II patients, 18–60 yr, undergoing orthopaedic surgery of the lower limb (table I). The study was approved by the Institutional Ethics Committee and informed verbal consent was obtained. Patients with cardiovascular diseases were excluded. The patients received diazepam 5–15 mg orally 1–1.5 h before induction of spinal anaesthesia. When required during surgery, diazepam 2.5–5 mg was given for sedation, or fentanyl 0.05–0.1 mg i.v. for analgesia. A midline lumbar puncture was performed at the L3–4 interspace using a 27-gauge needle with the patient in the lateral horizontal position. Plain 0.5% bupivacaine 3 ml at room temperature was injected. Thereafter the patients were turned gently to the supine horizontal position.

The cephalad spread of analgesia was assessed by pinprick. The segmental level of analgesia was recorded 60 min after injection of local anaesthetic, at the end of surgery and again after the patient was moved into bed (table I).

In the recovery room, the patient remained in the supine horizontal position for 15 min before the start of the study. All patients had a segmental level of the block in the range L1–T5 and the spinal block was stable or decreasing at the beginning of the test. The upper half of the patient's body was then tilted to a precalibrated, 30° head-up position. One of the

TABLE I. *Patient characteristics (mean (range)) and spread of spinal analgesia (median (range))*

Sex (M/F)	24/16
Age (yr)	43.4 (18–60)
Height (cm)	178.5 (153–192)
Weight (kg)	76.7 (49–109)
Segmental level of block	
60 min	T9 (L1–T2)
End of operation	T9 (L1–T4)
Arriving in recovery room	T9 (L1–T4)
Beginning of study	T10 (L1–T5)

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investigators assessed the segmental spread of spinal analgesia to pinprick at 5-min intervals for 30 min. The subjective sensations of the patient were also recorded. Arterial pressure (oscillotonometry) and heart rate were measured at 5-min intervals during surgery and the study and at 10-min intervals thereafter. ECG was monitored continuously. After the study, the patients were again placed horizontal.

Mann–Whitney *U* test was used to test the difference between times from the subarachnoid injection of local anaesthetic to the study.

RESULTS

In six of the 40 patients (15 %), increased cephalad spread of spinal analgesia was observed when the patients were placed in a 30° head-up position (fig. 1). The mean time from induction of spinal anaesthesia to the sit-up test was shorter in those six patients with an increase in the block (mean 92 min, range 80–115 min) than in the patients whose block did not change or was decreasing during the 30-min test (mean 119 min, range 83–210 min) ($P < 0.05$). The largest individual increase in spread was four segments. Two patients had a subjective sensation of an extension in block. One patient, who had an increase of one segment of the block (T12–T11) developed bradycardia (slowest heart rate 37 beat min^{-1}) and hypotension (smallest systolic pressure 75 mm Hg) and received atropine 0.5 mg i.v.

Five of the 40 patients had an extension of the block (two segments) after they were moved from the operation table to the bed. Only one of these patients belonged to the group of six patients who had extension of the block during the sit-up test, while the others had a regressing block. None of these five patients had any haemodynamic disturbances.

During the 30-min test, the level of spinal analgesia regressed in 29 patients and there was no change in five others. One of the patients, whose block regressed from T7 to T8 in 10 min after the change to sitting became hypotensive (systolic pressure 93/64 mm Hg) during the study and the study was interrupted.

The course of spinal anaesthesia during operation and recovery after the tilt test were uneventful.

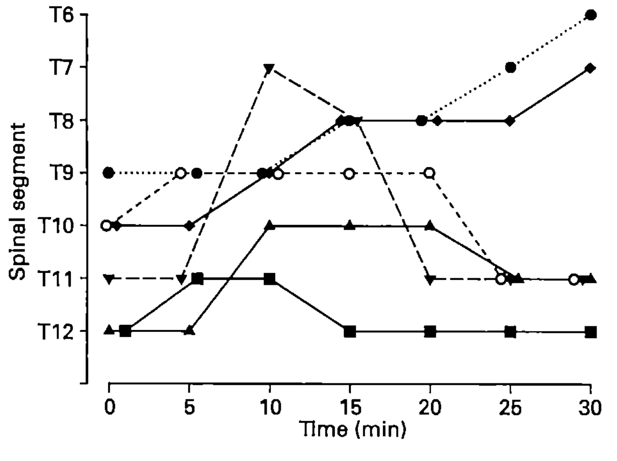

FIG. 1. Changes of segmental level of spinal anaesthesia in six patients during the study.

There were no major haemodynamic changes during surgery in any of the patients, and surgical blood loss was minimal. Nine patients received sedatives during induction of anaesthesia or surgery. One belonged to the group of six patients who had an extension of the block during the study. Only one patient received fentanyl (0.05 mg); he had an extension of block (one segment). In the recovery room, no sedatives or fentanyl were given before the tilt test.

DISCUSSION

To our surprise, in six patients, the level of spinal analgesia increased up to four segments when the patient was placed 30° head-up 80–115 min after the injection of bupivacaine. Thus it seems that there was still sufficient unbound bupivacaine in CSF to produce sensory block, probably by mechanically induced displacement of CSF in a cephalad direction. It is generally believed that the baricity of an injected solution influences the spread of local anaesthetic molecules for only approximately 30 min [12]. In spite of this, it has been shown that a change in the position of patients during spinal block with hyperbaric local anaesthetic solutions affects the spread of the block relatively late after induction [4, 5]. Block level has been found to extend by up to eight segments 60 min after administration of hyperbaric bupivacaine 4 ml when the patient was turned from the sitting to the supine horizontal position [5]. Also, the lateral position for 45 min after injection of 2 ml of hyperbaric 0.5 % bupivacaine, 5 % lignocaine or 4 % mepivacaine first produced unilateral anaesthesia, which changed to almost symmetrical bilateral anaesthesia when the patient was moved to the supine horizontal position [4].

Use of the sitting position during and after injection of plain bupivacaine (slightly hypobaric) produces a higher final level (by up to four segments) of block than use of the lateral horizontal position [13]. However, extending the duration of sitting from 2.5 to 7.5 min has not been found to influence the spread of the block [14], but a slow continuous increase was noticed for 30 min in all patients. This agrees with our present finding of changes up to 30 min, indicating late redistribution of the drug within the CSF. A slowly progressing extension of the block (promoted mainly by diffusion) has been observed in several studies [6–11] in which the time to the maximal level of analgesia was 60 min, or even later, with patients in a horizontal position. The continuous increase in the spread for the entire 30-min period in two of our patients (fig. 1) was similar to the diffusional type of distribution seen usually in the early phase of the block. In contrast, in the four other patients with extensions of block, the spread was probably caused by temporary cephalad displacement of CSF which contained a concentration of bupivacaine just sufficient to cause a block.

Only two of the patients had a decrease in heart rate and arterial pressure at the beginning of the 30-min sit-up test. The level and intensity of sympathetic block in relation to the level of sensory block may vary. Preganglionic sympathetic denervation occurs earlier and with smaller concentrations of local anaesthetic in the CSF than block of somatic sensory fibres [15]. Greene [17] suggested, therefore, that the sympathetic block extends two to four segments cephalad to the level of the sensory block. In contrast, Bengtsson, Löfström and Malmqvist [16] and Malmqvist and colleagues [17] have shown that the distribution of the sympathetic block may not exceed that of the sensory block during spinal anaesthesia. A change to the sitting position during sympathetic block of the lower half of the body may suddenly decrease the venous return to the heart. Acute activation of cardiac ventricular chemo- and mechanoreceptors (Bezold–Jarisch reflex) caused by the rapid decrease in ventricular volume has been suggested to be the aetiology of bradycardia in such instances. Atrial [18] or pacemaker stretch receptor reflexes [19] may also be involved. An extending sympathetic block possibly reaching the high thoracic level may impede the normal physiological compensatory cardiac response via unopposed vagal input. Unexpected bradycardia and even cardiac arrest have been documented in association with spinal anaesthesia without changes in position in patients with relatively high blocks [20–22]. As seen in our study, such cardiovascular complications may occur also when the sensory block reaches only the lower thoracic level.

Because the head-up tilt 80–115 min after subarachnoid injection increased the cephalad spread of the spinal block by one to four segments in six of our patients, we recommend the use of the supine horizontal position for patients during recovery and avoidance of unnecessary movements, when plain bupivacaine has been used for spinal anaesthesia.

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EFFECT OF EXTRADURAL DIAMORPHINE ON ANALGESIA AFTER CAESAREAN SECTION UNDER SUBARACHNOID BLOCK

C. J. ROULSON, J. BENNETT, M. SHAW AND F. CARLI

SUMMARY

We have examined the efficacy, duration of action and side effects of extradural diamorphine alone and in combination with 1:200000 adrenaline in a randomized, double-blind controlled study of 45 patients who underwent Caesarean section under spinal anaesthesia. Saline 10 ml, diamorphine 2.5 mg in saline 10 ml or diamorphine 2.5 mg in 1:200000 adrenaline 10 ml were administered via the extradural route at delivery of the baby. Both diamorphine and diamorphine with adrenaline provided significantly prolonged analgesia compared with control (mean time to next analgesia (95% confidence interval) 17.3 h (12.0, 22.1 h), 15.9 h (10.6, 21.1 h), 5.7 h (1.5, 9.9 h), respectively) (P < 0.01). The addition of adrenaline increased the quality of analgesia 8 h after operation, but had no effect on the total amount of i.m. morphine administered during the first 24 h. The incidence of side effects was similar in all groups. (Br. J. Anaesth. 1993; **71**: 810–813)

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques, regional: extradural, spinal. Analgesics: diamorphine.

Although subarachnoid block is the method used most frequently to provide regional anaesthesia for lower segment Caesarean section in the U.S.A. [1], it has only recently become a popular technique in the U.K. Its major advantages compared with extradural anaesthesia include speed of onset of a reliable surgical block and the excellent muscle relaxation provided.

The disadvantage of a "single-shot" subarachnoid technique lies in its inflexibility. In contrast, the use of combined spinal–extradural anaesthesia enables the anaesthetist to improve an inadequate block, prolong the duration of anaesthesia if required and give the patient a further extradural increment of local anaesthetic or opioid to provide postoperative analgesia [2–4].

Because diamorphine is not widely available for clinical use outside the U.K., there are fewer studies investigating its use than those using morphine. However, diamorphine has a greater lipid solubility than morphine (olive oil/water partition coefficient of diamorphine 0.2 *vs* morphine 0.016 [5]) and is more rapidly transferred across membranes from the extradural space to spinal cord receptors. This results in a faster onset time of analgesia [6] and limits the potential for rostral spread of diamorphine within the cerebrospinal fluid causing delayed respiratory depression.

When compared with i.m. diamorphine, extradural diamorphine has been shown to provide an improved quality of analgesia after Caesarean section under extradural anaesthesia [7]. The addition of adrenaline appears to extend the duration of analgesia without altering the incidence of side effects [7, 8].

The present study was designed to assess the quality and duration of pain relief provided by subarachnoid anaesthesia combined with post-delivery extradural diamorphine. In addition, we have examined the effect of adding adrenaline to the extradural diamorphine.

PATIENTS AND METHODS

Hospital Ethics Committee approval was obtained. After obtaining informed consent, we studied 45 patients requiring either elective or emergency Caesarean section who did not have a functioning extradural *in situ*. In the operating theatre an i.v. cannula was inserted and Hartmann's solution 500–1000 ml was administered rapidly to maintain a systolic arterial pressure greater than 100 mmHg measured non-invasively. An 18-gauge Tuohy needle was inserted at either the L2–3 or the L3–4 interspace with the patient in the left lateral position. With the Tuohy needle in the extradural space, a 15-cm 25-gauge Whitacre (Becton Dickinson) spinal needle was guided through it to enter the subarachnoid space. After intrathecal administration of 0.5% hyperbaric bupivacaine 2.2 ml, an extradural catheter was placed 3.0 cm into the extradural space and secured to the back, then the patient was turned immediately to the right lateral position. Before commencement of surgery, all patients developed a sensory block to T4 which was adequate for the comfortable completion of surgery. Patients were excluded from the study when inadequate subarachnoid block occurred requiring extradural supplementation.

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TABLE I. *Patient characteristics in the three groups studied (mean (SD) [range])*

	Control ($n = 15$)	Diamorphine ($n = 15$)	Diamorphine + adrenaline ($n = 15$)
Age (yr)	32.5 [23–43]	30.6 [24–45]	33.4 [27–41]
Weight (kg)	70.9 (12.4) [55–89]	77.3 (19.7) [46–127]	67.3 (10.4) [53–85]
Height (m)	1.57 (0.07) [1.48–1.70]	1.60 (0.08) [1.45–1.78]	1.60 (0.05) [1.50–1.68]
Emergency/ Elective	4/11	4/11	4/11

TABLE II. *Postoperative analgesia and adverse effects (mean (SE) [95% confidence interval]). ** Significant difference (P < 0.01) compared with diamorphine and diamorphine + adrenaline groups*

	Control ($n = 15$)	Diamorphine ($n = 15$)	Diamorphine + adrenaline ($n = 15$)
Time to next analgesia (h)	5.7 (2.0) [1.5, 9.9]**	17.3 (2.3) [12.0, 22.1]	15.9 (2.4) [10.6, 21.1]
24-h morphine requirement (mg)	16.0 (2.7) [10.1, 21.9]	6.7 (2.7) [0.9, 12.5]	9.3 (3.0) [2.9, 15.8]
Visual analogue score (cm)			
Pain			
2 h post-op.	3.3 (0.8) [1.6, 5.0]	0.4 (0.2) [0.01, 0.8]	0.8 (0.4) [−0.1, 1.7]
8 h post-op.	2.9 (0.5) [1.9, 3.9]	1.8 (0.7) [0.4, 3.2]	1.3 (0.4) [0.5, 2.0]
24 h post-op.	2.3 (0.5) [1.2, 3.4]	2.2 (0.6) [0.9, 3.5]	3.5 (0.7) [1.9, 5.0]
Sedation			
2 h post-op.	2.0 (0.9) [0.1, 3.8]	1.9 (0.7) [0.4, 3.3]	4.6 (1.1) [2.3, 6.9]
8 h post-op.	1.5 (0.6) [0.2, 2.8]	1.8 (0.9) [−0.1, 3.7]	4.2 (0.8) [2.6, 5.8]
24 h post-op.	1.9 (0.8) [0.1, 3.7]	1.2 (0.6) [−0.2, 2.6]	1.9 (0.5) [0.8, 3.1]
Adverse effects			
Nausea	2	4	3
Vomiting	2	3	3
Itching	2	5	8

After delivery of the baby, the patients were allocated to three groups: group 1 (control) ($n = 15$), received 0.9% NaCl 10 ml; group 2 ($n = 15$) received diamorphine 2.5 mg made up to a volume of 10 ml with 0.9% NaCl; group 3 ($n = 15$) received diamorphine 2.5 mg made up to a volume of 10 ml with 1:200000 adrenaline.

The paediatrician attending the operation opened a numbered, sealed envelope and prepared the named trial drug. This was administered via the extradural route by the anaesthetist, who was unaware of the nature of the solution. At the end of the operation, the extradural catheter was removed. Postoperative analgesia comprised morphine 10 mg i.m. and oral paracetamol 1 g to be administered as required.

A questionnaire was given to all patients and consisted of ungraduated 10-cm visual analogue scales to be marked for pain and sedation 2, 8 and 24 h after surgery. At 24 h, information on the incidence of itching, nausea, vomiting and urinary retention was obtained by direct questioning of the patient. The time from completion of surgery to the first administration of postoperative analgesia and the total dose of i.m. morphine received within the first 24 h after operation were recorded.

Statistical analysis

Analysis of variance was used to compare patient details and the 24-h i.m. morphine requirement. The Mann–Whitney *U* test was used to compare the duration of analgesia between groups and the linear analogue pain and sedation scores. No correction was made for repeated measures analysis. Chi-square tests were used to compare the incidence of nausea, itching and vomiting. $P < 0.05$ was considered statistically significant.

RESULTS

Patients in each group were of similar age and height, but the weight range varied most in those receiving diamorphine (table I); there were no significant differences between the three groups. Eleven of the 15 patients in each group underwent elective Caesarean section, the remainder having emergency surgery. The main indications for Caesarean section were repeat procedure, breech position and transverse lie of the fetus.

Two patients who consented to inclusion in the study required extradural bupivacaine in order for surgery to proceed. These patients were excluded from the study and their study envelopes were allocated to other patients to produce a total of 45 women. Anaesthesia was obtained satisfactorily with 0.5% bupivacaine 2.2 ml and provided a minimum sensory block to T4 and acceptable operating conditions in all 45 women. Values measured and derived from the visual analogue pain and sedation scores are given in table II. Postoperative analgesia was considered to be satisfactory if the pain score on the visual analogue scale was less than 2.5 cm (fig. 1). At 2 h, patients in the control group scored themselves significantly more for pain than either of the treatment groups ($P < 0.01$). At 8 h, analgesia was significantly better in the group receiving diamorphine and adrenaline ($P = 0.013$). The difference between the control group and those

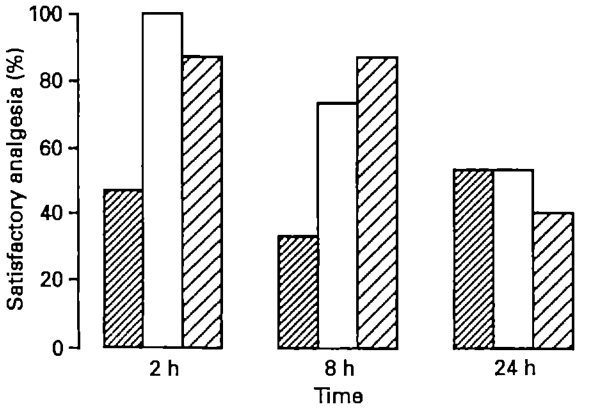

FIG. 1. Percentage of patients with satisfactory postoperative analgesia (score < 2.5 cm on an ungraduated 10-cm visual analogue scale). ▨ = Control; ☐ = diamorphine; ▨ = diamorphine + adrenaline.

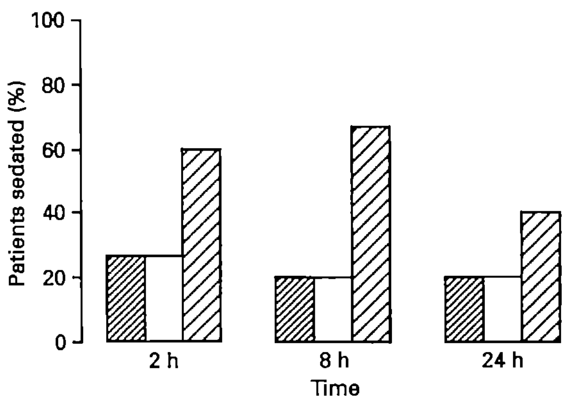

FIG. 2. Percentage of patients significantly sedated (score > 2.5 cm on an ungraduated 10-cm visual analogue scale). ▨ = Control; ☐ = diamorphine; ▨ = diamorphine + adrenaline.

receiving diamorphine did not achieve significance ($P = 0.055$). The two groups receiving diamorphine with or without adrenaline did not differ significantly ($P = 0.95$). At 24 h after surgery there were no significant differences between groups. The time to first postoperative analgesia was considerably prolonged in both treatment groups compared with the control group ($P < 0.01$) (table II). The 24-h morphine requirement was greatest in the control group and least in the group receiving diamorphine (ns).

A patient was considered sedated if she scored herself at greater than 2.5 cm on the 10-cm visual analogue sedation scale. On this basis, patients in the control and diamorphine groups were sedated similarly at all evaluation times, with maximum sedation recorded 2 h after operation (fig. 2). Patients in the group receiving diamorphine and adrenaline were more sedated 8 h after operation ($P < 0.05$) than either of the other groups, but sedation was comparable in all groups at 2 h and 24 h.

The groups did not differ in nausea or vomiting, although fewest side effects occurred in the control group and, whilst the control group suffered least from itching and the diamorphine and adrenaline group most, these differences were not significant ($0.1 > P > 0.05$).

DISCUSSION

The findings of this study corroborate the analgesic efficacy of administering diamorphine via the extradural route after Caesarean section: the mean time to first analgesia was almost trebled in both treatment groups compared with the control group.

The combined technique, in which a subarachnoid injection was given before placement of the extradural catheter, provided good operating conditions very rapidly, with the facility to improve upon an inadequate block when necessary [2–4].

In a previous study at this institution [7], women received extradural diamorphine 2.5 or 5 mg with or without adrenaline when pain returned after Caesarean section under extradural anaesthesia. In the group receiving diamorphine 2.5 mg, the time to next analgesia was mean 4.76 h (range 1.0–12.5 h). The addition of adrenaline prolonged the time to next analgesia to 6.05 h (range 1.5–24.0 h). Similarly in the groups receiving diamorphine 5 mg, addition of adrenaline prolonged the time to next analgesia from 5.7 h (range 1.75–13.3 h) to 7.2 h (range 1.6–26.5 h). In contrast with the previous study, the mean times to next analgesia in the groups receiving diamorphine 2.5 mg by the extradural route without and with adrenaline in our study were 17.3 and 15.9 h, respectively.

It is unlikely that the difference in mean time to next analgesia was a result of the different timing of administration of the extradural diamorphine. In our study diamorphine was provided by the extradural route immediately on delivery of the baby, whereas Smith and colleagues [7] recorded time to next analgesia from the patient's postoperative request for pain relief (when diamorphine was administered by the extradural route), at which time the block was receding. Another possible explanation may be the type and quality of conduction block provided. Smith's group used extradural block for Caesarean section. The more profound sensory block initially associated with the use of subarachnoid block in our study may have decreased the severity of the patient's postoperative pain by preventing the development of neuroexcitability and pain patterning, as shown in other studies [9, 10]. Lastly, the presence of the hole made in the dura by the spinal needle may have permitted a greater percentage of the diamorphine injected by the extradural route to be transferred through to the cerebrospinal fluid and fixed by the neural tissue.

Another difference between the two studies is the finding by Smith and colleagues [7] that the addition of adrenaline to diamorphine prolonged the time to the next analgesia. However, they found that, whilst there was a tendency to prolonged analgesia with adrenaline, the only significant difference was between groups receiving diamorphine 2.5 mg alone and those given diamorphine 5.0 mg with adrenaline ($P < 0.05$). The effect of adding adrenaline is not further clarified by the present study. At 2 and 24 h, the group receiving diamorphine alone had better analgesia, whilst at 8 h analgesia was superior in the group receiving adrenaline. Differences between these two groups were not significant at any time of measurement. By causing vasoconstriction of the extradural veins, adrenaline decreases the amount of diamorphine absorbed systemically [11], thus effectively increasing the concentration available in the extradural space and thus we expected more prolonged analgesia in the women receiving adrenaline. The small numbers in each group may account for why we did not find this. As a corollary of decreased systemic absorption, one would expect to find less sedation in the adrenaline group than in the group receiving diamorphine alone. Unexpectedly, patients in the adrenaline group were significantly more sedated than those in the other groups at 8 h after the operation. This may reflect the superior analgesia experienced at this time or possibly, in common with clonidine, extradural adrenaline may, as an alpha agonist, have some sedative effect in its own right [12].

The incidence of side effects was comparable between groups. Other studies [13] have demonstrated an increased incidence of nausea, vomiting and itching in patients given extradural opioids. Itching appeared to be increased in both treatment groups compared with control, but this was not significant because of the relatively small numbers in each group. No patient complained of urinary retention or postural headache on direct questioning the following day.

In conclusion, extradural diamorphine provided prolonged analgesia after Caesarean section under subarachnoid anaesthesia. Addition of adrenaline had little effect on the quality or duration of analgesia in the women studied. Initial subarachnoid rather than extradural block may also increase the duration of postoperative analgesia.

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ORAL BROMFENAC 10 AND 25 MG COMPARED WITH SUBLINGUAL BUPRENORPHINE 0.2 AND 0.4 MG FOR POSTOPERATIVE PAIN RELIEF

D. CARROLL, T. FRANKLAND, C. NAGLE AND H. McQUAY

SUMMARY

The aim of this single-dose, randomized, positive control, double-dummy, double-blind, parallel group study was to compare oral bromfenac 10 and 25 mg with sublingual buprenorphine 0.2 and 0.4 mg for treatment of postoperative pain. We studied 91 patients with moderate or severe pain after general surgical or orthopaedic operations, using pain intensity, pain relief, adverse effect, mood and sedation outcomes. There was a significant analgesic dose–response for buprenorphine, showing study sensitivity, but not for bromfenac. The two bromfenac treatments were significantly superior to the two buprenorphine treatments. Significantly more patients reported nausea with buprenorphine. There was evidence of a ceiling effect for analgesia with bromfenac. (Br. J. Anaesth. 1993; **71**: 814–817)

KEY WORDS

Analgesics, non-opioid: bromfenac. Analgesics, opioid: buprenorphine. Pain: postoperative.

The precise roles of the two drug classes, opioids and non-steroidal anti-inflammatory drugs (NSAID), in the management of postoperative pain remain contentious. For many years opioids were the only injectable analgesics available, but the introduction of injectable NSAID has encouraged wider use of NSAID immediately after surgery. Oral opioids have a poor reputation for postoperative pain control [1], but there is strong evidence from randomized controlled trials for the effectiveness of oral NSAID in treating postoperative pain [2, 3].

The evidence from single-dose randomized controlled trials suggests that injectable NSAID can provide analgesia indistinguishable from that obtained with injected opioids [4], and that oral NSAID can also match the effect of an injected opioid [5]. However, a ceiling effect has been demonstrated for NSAID analgesic effect [5, 6] by both oral [6] and injected routes [7].

This study was designed to compare oral bromfenac, a new 2-amino-3-benzoylphenylacetic acid derivative NSAID, with an opioid, sublingual buprenorphine, for the treatment of postoperative pain.

Bromfenac has anti-inflammatory, antipyretic and analgesic properties. In a previous study of pain after dental extraction, bromfenac in doses of 5, 25 and 50 mg was significantly better than placebo and the 25- and 50-mg doses were also significantly superior to aspirin 650 mg [8]. Bromfenac 5, 10 and 25 mg was also compared with paracetamol 1 g and placebo for pain relief after orthopaedic surgery; the 5-mg dose of bromfenac was superior to placebo and the 10-mg dose was equivalent to paracetamol 1 g [2].

PATIENTS AND METHODS

This was a double-blind, double-dummy, parallel group, single-dose study, comparing oral bromfenac 10 or 25 mg with sublingual buprenorphine 0.2 or 0.4 mg. It was approved by the Central Oxford Research Ethics Committee. Men and women were eligible for the study if they were to undergo orthopaedic or general surgery. Patients were excluded if they had a history of peptic ulcer disease, hepatic or renal disease, intolerance to aspirin, buprenorphine or NSAID, respiratory disease sufficient to contraindicate the use of buprenorphine, or if they were taking coumarin-type anticoagulants or oral hypoglycaemic agents. Women were excluded if they were pregnant or breast feeding.

Patients experiencing moderate or severe pain (verbal rating scale) within 72 h of surgery were included if they had recovered sufficiently from surgery, were capable of taking oral medication, and if more than 3 h had elapsed since they had received any analgesic, tranquillizing or sedative drug. They were allocated to one of four groups: sublingual buprenorphine 0.2 mg (one buprenorphine 0.2 mg tablet, one placebo sublingual tablet and one placebo oral capsule); sublingual buprenorphine 0.4 mg (two buprenorphine 0.2 mg tablets and one placebo oral capsule); oral bromfenac 10 mg (two placebo sublingual tablets and one bromfenac 10 mg capsule); oral bromfenac 25 mg (two placebo sublingual tablets and one bromfenac 25 mg capsule).

Tablets and capsules were identifiable only by treatment number. Randomization was stratified at entry by initial pain intensity ("moderate" or

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"severe") and by type of surgery (general or orthopaedic). Randomization was in blocks of four, organized by random number generation.

A nurse observer administered all the study treatments. The oral capsule was given first and swallowed with water 100 ml, which was followed immediately by the two sublingual tablets, which were allowed to dissolve under the tongue. Patients were then assessed for up to 6 h after receiving the study treatment. If pain relief was inadequate after the first 1 h, patients were free to request further analgesia and standard postoperative analgesia was given.

Baseline assessments of patients were made for pain intensity, vital signs, mood and sedation. All assessments were made by one nurse observer (T.F.). Patients were reassessed at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h. Pain intensity, vital signs, mood and sedation assessments were repeated, together with assessments for pain relief and adverse effects. At the end of the 6-h study period, or at the time of remedication, an overall rating of the treatment was made by the nurse and by the patient.

Current pain intensity was measured by a categorical verbal rating scale (0 = none; 1 = mild; 2 = moderate; 3 = severe) using the question "how intense is the pain at the moment?"; by an eight-word scale (randomly placed words ranging from "no pain" to "excruciating", scored 0–7) [9], by a visual analogue scale (100-mm line, left end labelled "no pain" and right end labelled "worst possible pain") and by the McGill Pain Questionnaire using 78 descriptors in 20 groups.

Pain relief was measured by a categorical verbal rating scale (0 = none; 1 = slight; 2 = moderate; 3 = good; 4 = complete) using the question "How much pain relief have you got at the present time?"; and by a visual analogue scale (100-mm line, left end labelled "no relief of pain" and right end labelled "complete relief of pain").

Mood was measured with a visual analogue scale (100-mm line, left end labelled "worst I could feel" and right end labelled "best I could feel"). Sedation was measured by a categorical verbal rating scale (0 = alert; 1 = mildly drowsy; 2 = moderately drowsy; 3 = asleep). If patients were asleep, they were wakened for assessments. Systemic arterial pressure, heart rate and ventilatory frequency were measured by the nurse observer.

At the end of the 6-h study period, or at the time patients asked to withdraw from the study, both the nurse observer and the patient made a global rating of the study treatment (0 = poor; 1 = fair; 2 = good; 3 = very good; 4 = excellent). The nurse made her evaluation first, to avoid bias. Adverse effects, both volunteered and observed, were recorded, with scoring of intensity (0 = none; 1 = mild; 2 = moderate; 3 = severe).

Statistical analysis

It was estimated that 20 patients per group would be necessary to achieve power of 90% with an alpha level of 0.05 (one-tailed) to detect a difference between the four treatments of 1.5 on the categorical pain relief with SD of 0.3 [2].

Patients who were remedicated within the 6-h study period were given initial values of pain intensity and a pain relief score of zero for assessment times after remedication [10]. The McGill pain questionnaire was scored both for number of words chosen and for sum rank score. The sum of the pain intensity difference (four word SPID) and total pain relief (TOTPAR) scores were calculated [11], to produce an area under the curve of effect against time. The same calculation was used for the visual analogue equivalents (VASSPID for pain intensity and VASPR for pain relief), the eight-word verbal rating for pain intensity (WORDSPID) and the McGill word and total scores (McGill wordSPID and McGill scoreSPID, respectively). The overall sedation and mood scores (AUCSEDATION and AUCMOOD) were calculated by use of a trapezoidal formula.

Analysis of variance was used on the scores for the four treatments groups, and the Student's t test was used for comparisons of pairs—one-tailed within drug between doses and two-tailed between drug. The incidence of adverse effects and time to remedication were compared using the chi-square test. All tests were performed using Statview 4 on a Macintosh IIci. Results are presented as mean (SEM).

RESULTS

We studied 91 patients between November 1989 and February 1991. Three patients did not fulfil the study design. Of these three, one was excluded from the final analysis, because she received additional analgesia at the 0.5-h assessment. Two were included: one developed a headache, thought to be caused by a dural tap, and was given paracetamol; the other inadvertently received an NSAID during the study. Their results to the time of remedication were included in the analysis (i.e. the same strategy as for other patients who were remedicated during the 6-h study period).

Details of the patients are shown in table I; there were no significant differences between the four groups in age, sex, height, weight or duration of surgery (ANOVA).

Analgesic measures (table II)

There were statistically significant differences between the four groups for all analgesic outcome measures (ANOVA). Sublingual buprenorphine 0.4 mg gave significantly better analgesia than 0.2 mg on all analgesic outcome measures except for the patient and nurse global rating (one-tailed t test); there were no significant differences between the 10- and 25-mg doses of oral bromfenac (one-tailed t test).

Bromfenac 10 mg provided significantly better analgesia than both doses of buprenorphine on all analgesic measures (two-tailed t test). Bromfenac 25 mg provided significantly better analgesia than buprenorphine 0.2 mg on all measures, but was significantly better than buprenorphine 0.4 mg only for SPID, WORDSPID and patient global rating. The rank order was thus buprenorphine 0.2 mg < buprenorphine 0.4 mg < bromfenac 10 and 25 mg.

TABLE I. *Patient characteristics, and duration and nature of surgical procedure (mean (range or* SEM*)). No significant difference between treatments overall (ANOVA)*

	Buprenorphine		Bromfenac	
	0.2 mg	0.4 mg	10 mg	25 mg
No. patients	22	24	23	21
Age (yr)	41 (18–61)	38 (19–63)	43 (23–69)	43 (20–65)
Sex (F:M)	13:9	12:12	16:7	9:13
Height (cm)	170 (2)	170 (2)	168 (2)	173 (2)
Weight (kg)	69 (2)	69 (3)	68 (3)	75 (3)
Surgery time (min)	68 (8)	79 (10)	62 (7)	73 (7)
Surgical procedure				
Orthopaedic	15	15	16	14
General surgery	7	7	7	7

TABLE II. *Analgesic outcome measures (mean (*SEM*)). Significant differences: *overall between the four treatment groups (ANOVA); †between 0.2 and 0.4 mg buprenorphine (one-tailed* t *test); ‡between bromfenac 10 mg and buprenorphine 0.2 mg (two-tailed* t *test); §between bromfenac 10 mg and buprenorphine 0.4 mg (two-tailed* t *test); ¶between bromfenac 25 mg and buprenorphine 0.2 mg (two-tailed* t *test); ‖between bromfenac 25 mg and buprenorphine 0.4 mg (two-tailed* t *test); **(chi-square)*

	Buprenorphine		Bromfenac		
	0.2 mg	0.4 mg	10 mg	25 mg	
No. patients	22	24	23	21	
SPID	1.8 (0.4)	3.1 (0.6)	6.4 (0.9)	5.5 (1.0)	*†‡§¶‖
VASSPID	41 (13)	92 (19)	175 (24)	122 (29)	*†‡§¶
TOTPAR	5.2 (0.8)	8.5 (1.2)	14.1 (1.3)	11 (1.7)	*†‡§¶
VASTOTPAR	156 (26)	242 (34)	386 (33)	317 (45)	*†‡§¶
WORDSPID	2.9 (0.6)	5.4 (1)	12 (1.8)	10 (1.9)	*†‡§¶‖
McGill WORDSPID	1.3 (0.7)	6.3 (1.9)	13.6 (2.3)	10.2 (2.6)	*†‡§¶
McGill SCORESPID	7.5 (3.6)	20.2 (4.6)	34.7 (5.4)	28.9 (7.9)	*†‡§¶
Patient global	1.4 (0.2)	1.8 (0.2)	2.9 (0.2)	2.4 (0.3)	*‡§¶‖
Nurse global	1.2 (0.2)	1.6 (0.3)	2.5 (0.2)	2.5 (0.2)	*‡§¶
Completing study	4	11	14	12	**
AUCSEDATION	2.6 (1)	2.6 (0.8)	2.7 (0.8)	2.5 (1.1)	
AUCMOOD	344 (43)	553 (61)	819 (54)	697 (86)	*†‡§¶

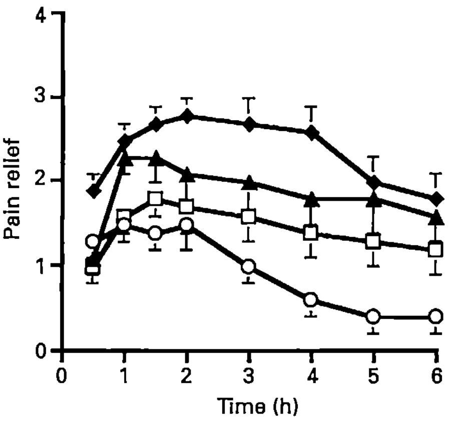

FIG. 1. Mean (SEM) pain relief against time for buprenorphine 0.2 mg (○), buprenorphine 0.4 mg (□), bromfenac 10 mg (◆) and bromfenac 25 mg (▲). Significant differences at all times after 30 min (ANOVA).

Mean categorical verbal pain relief scores against time for the four groups reflect this rank order (fig. 1).

Non-analgesic outcome measures

There was a significant difference overall between the four treatment groups for AUCMOOD, with significantly greater mood scores with buprenorphine 0.4 mg than with 0.2 mg (one-tailed *t* test). Bromfenac 10 mg provided significantly greater mood scores than either dose of buprenorphine (two-tailed *t* test) and AUCMOOD with bromfenac 25 mg was significantly greater than with buprenorphine 0.2 mg, but not buprenorphine 0.4 mg. There was no significant difference between the AUCMOOD scores for bromfenac 10 and 25 mg.

There was no significant difference overall between the four treatment groups for AUCSEDATION.

Adverse effects

More patients reported adverse effects after buprenorphine; twice as many patients (eight) had adverse effects with buprenorphine 0.2 mg compared with bromfenac 25 mg. The incidence of nausea was significantly greater with buprenorphine 0.4 mg, with five patients affected compared with none who received bromfenac ($P < 0.02$, chi-square).

Time to remedication

There was a statistically significant difference between the treatments for the number of patients who needed remedication before the end of the study ($P < 0.02$, chi-square). Only four patients who received the smaller dose of buprenorphine completed the 6-h study. In all but the two patients described above, this was because of inadequate pain relief and they were remedicated with standard analgesia.

DISCUSSION

The sensitivity of the study was demonstrated by the dose–response for sublingual buprenorphine—0.4 mg provided significantly better analgesia than 0.2 mg on all of the analgesic outcome measures (table II). Few other randomized, controlled trials have examined the dose–response for sublingual buprenorphine. In one such comparison of sublingual buprenorphine 0.2, 0.4 and 0.8 mg with i.m. morphine 4, 8 and 16 mg, a significant dose–response for sublingual buprenorphine was found, with a potency ratio to morphine of 1:15 [12].

Oral bromfenac provided better analgesia than sublingual buprenorphine (table II, fig. 1). Both 10- and 25-mg doses of bromfenac produced significantly better analgesia than the larger dose of buprenorphine (0.4 mg). Previous studies have suggested that oral NSAID provide better analgesia than i.m. opioids; oral ketoprofen 75 and 225 mg was equal to or more effective than i.m. morphine 5 and 10 mg [5]. It is perhaps less surprising, then, that oral bromfenac 10 mg was superior to sublingual buprenorphine 0.4 mg, and suggests that 0.8 mg would be necessary to provide equivalent analgesia, with an increased risk of unacceptable adverse effects.

There was no evidence of a dose–response for bromfenac; indeed, the analgesic scores for 10 mg were better than those for 25 mg on most outcomes. Such ceiling effects with NSAID have been reported previously in single-dose analgesic studies [5]; occasionally with NSAID, a dose–response is found for duration of analgesia, although not apparent on peak or total (TOTPAR) analgesia during the study period. The clinical conclusion is that in this setting there would be no advantage in giving bromfenac 25 mg rather than 10 mg. Bromfenac, in common with other oral NSAID, proved to be an effective analgesic for moderate or severe postoperative pain. The lesser incidence of adverse effects with NSAID compared with opioids at equivalent (or better) levels of pain relief suggests that oral NSAID should be used more in the management of postoperative pain.

ACKNOWLEDGEMENTS

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PATIENT-CONTROLLED ANALGESIA WITH LOW DOSE BACKGROUND INFUSIONS AFTER LOWER ABDOMINAL SURGERY IN CHILDREN

E. DOYLE, I. HARPER AND N. S. MORTON

SUMMARY

Forty-five children (aged 6–12 yr) undergoing appendicectomy received one of three analgesic regimens using patient-controlled analgesia (PCA) with morphine: no background infusion (B0); background infusion 4 μg kg^{-1} h^{-1} (B4); background infusion 10 μg kg^{-1} h^{-1} (B10). Total consumption of morphine was greater in group B10 compared with groups B0 ($P < 0.01$) and B4 ($P < 0.05$). There was no significant difference in morphine consumption in groups B0 and B4. All three groups self-administered similar amounts of morphine and there were no significant differences in pain scores or incidence of excessive sedation. Group B4 suffered less hypoxaemia compared with groups B0 ($P < 0.01$) and B10 ($P < 0.001$). Group B10 suffered more nausea and vomiting than groups B0 ($P < 0.001$) and B4 ($P < 0.001$), but there was no significant difference in the incidence of nausea and vomiting between groups B0 and B4. Groups B4 and B10 spent more time at night asleep than group B0 ($P < 0.05$). There were no significant differences between the groups in the amount of time spent asleep during the day. Inclusion of a background infusion of morphine 4 μg kg^{-1} h^{-1} in a PCA regimen for children did not increase the incidence of side effects and was associated with less hypoxaemia and a better sleep pattern than no background infusion. (Br. J. Anaesth. 1993; **71**: 818–822)

KEY WORDS

Analgesia: patient-controlled. Vomiting, nausea.

Patient-controlled analgesia (PCA) is now used in children as young as 5 yr for the treatment of postoperative pain [1]. The drug used most commonly is morphine, in a bolus dose of 10–25 μg kg^{-1} and a lockout interval of 5–15 min. These settings are empirical and there are few well conducted studies which have compared different PCA regimens in paediatric practice. In particular, the benefits and risks of background infusions have not been defined. Adult studies give conflicting results [2–6] and one study in children [7] found an improvement in analgesia without an increase in side effects with a background infusion of morphine 15 μg kg^{-1} h^{-1}. A more recent paediatric study [8] found that a background infusion of morphine 20 μg kg^{-1} h^{-1} did not improve pain scores, but was associated with a better sleep pattern. However, the background infusion was associated with a greater incidence of hypoxaemia, excessive sedation, nausea and vomiting compared with the PCA-only regimen.

This study was carried out to assess the effect of two different low-dose background infusions on postoperative analgesia, sleep pattern, morphine consumption, sedation, nausea, vomiting, respiratory depression and arterial oxygen saturation in air (Sp_{O_2}).

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained. On the basis of previous work using this methodology [8], it was calculated that this study had a 90% probability of detecting differences between groups which would be significant at the 5% level. Forty-five children aged 6–12 yr undergoing appendicectomy were recruited. Patients were visited before operation, when the principles of using PCA were explained to the child and parents. Patients were taught to use the trigger of the PCA machine during this visit. Patients were not studied if they had received preoperative analgesia.

All patients received a standard general anaesthetic which comprised rapid sequence induction with thiopentone 5–7 mg kg^{-1} and suxamethonium 1 mg kg^{-1}. The trachea was intubated and the patient's lungs ventilated with 67% nitrous oxide and 0.5–2.0% isoflurane in oxygen as indicated clinically. Neuromuscular block was maintained with vecuronium 0.1 mg kg^{-1}. Morphine 0.1 mg kg^{-1} was given during operation. At the end of surgery, neuromuscular block was antagonized with neostigmine and glycopyrronium in appropriate doses. In the recovery area, patients were made comfortable with boluses of morphine 50 μg kg^{-1} if required.

Before the patient left the recovery area, the PCA pump was set up (Graseby PCAS and Graseby 3300). The solution consisted of morphine 1 mg kg^{-1}

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TABLE I. *Patient characteristics and details of morphine consumption (mean (range or* SD*)). Significant differences compared with group B10*: *$P < 0.05$; **$P < 0.01$

	Group B0	Group B4	Group B10
Sex (M:F)	7:8	8:7	10:5
Age (yr)	10.5 (8.7–12.1)	10.4 (6.5–12.9)	10.3 (7.2–12.4)
Weight (kg)	35.5 (9.0)	35.9 (6.8)	40.0 (10.7)
Time of operation			
06:00–22:00	10	9	10
22:00–06:00	5	6	5
Duration of PCA use (h)	38.5 (5.2)	42.7 (9.5)	45.4 (12.6)
Total morphine consumption			
(μg kg^{-1})	880 (389)**	1080 (467)*	1524 (619)
(μg kg^{-1} h^{-1})	23.5 (10.8)**	25.4 (9.2)*	35.9 (18.9)
Self-administered morphine			
(μg kg^{-1})	880 (389)	910 (452)	1062 (638)
(μg kg^{-1} h^{-1})	23.5 (10.8)	21.4 (9.2)	25.9 (18.9)

diluted to 50 ml with 0.9% saline (20 μg kg^{-1} ml^{-1}). The PCA machine was attached to the side arm of a Cardiff one-way valve incorporated into the i.v. infusion cannula. Patients were allocated randomly (computer-generated list) to receive one of three different PCA regimens: group B0 received bolus doses of morphine 20 μg kg^{-1} with a lockout interval of 5 min and no background infusion; group B4 received bolus doses of 20 μg kg^{-1} with a lockout interval of 5 min and a background infusion of morphine 4 μg kg^{-1} h^{-1}; group B10 received bolus doses of 20 μg kg^{-1} with a lockout interval of 5 min and a background infusion of 10 μg kg^{-1} h^{-1}.

After operation, patients breathed air and a monitoring regimen described previously [9] was used. This involved a high dependency level of nursing care with hourly recordings of Sp_{O_2}, ventilatory frequency and sedation, pain and nausea scores. The number of demands made and the volume of solution infused were also recorded hourly. Patients were reviewed regularly by one of the authors. There was always a named anaesthetist available to deal with any problems relating to the PCA regimen. PCA was discontinued when there was a consistent decline in use and the patient was able to take oral analgesics.

Pain was measured using a four-point, self-reporting score which has been validated previously [10]: 0 = no pain; 1 = not really sore; 2 = quite sore; 3 = very sore.

Children were not awakened from sleep for assessment unless the nurse suspected excessive sedation and "A" was recorded on the chart at these times. Sedation was scored using a four-point scale: 0 = eyes open spontaneously; 1 = eyes open to speech; 2 = eyes open when shaken; 3 = unrousable.

We considered patients to be sedated excessively if they were not rousable by speech and required to be shaken. Experienced paediatric nurses were able to differentiate between a child who was asleep naturally and one who was sedated excessively as a result of opioid.

Nausea was scored on a four-point scale: 0 = none; 1 = nausea only; 2 = vomited once in the past 1 h; 3 = vomited more than once in the past 1 h.

If there was a pain score of 3, a sedation score of 3 or a nausea score of 3, the named anaesthetist was asked to see the patient.

Results were analysed using analysis of variance and the Mann–Whitney U test for pain scores and morphine consumption, and chi-square tests for comparisons of events between groups.

RESULTS

Patient characteristics are shown in table I.

Two patients in group B0, one in group B4 and one in group B10 received a bolus of morphine 50 μg kg^{-1} in the recovery area. These boluses were not included in the figures for postoperative consumption of morphine.

Patients in all three groups self-administered similar amounts of morphine using the PCA machine. Total morphine consumption was significantly greater in group B10 compared with groups B0 ($P < 0.01$) and B4 ($P < 0.05$). Group B4 self-administered 2 μg kg^{-1} h^{-1} less than group B0; thus when the background infusion is taken into account, group B4 received 2 μg kg^{-1} h^{-1} more morphine than group B0.

For each patient, the hourly pain scores during each 4-h period after the start of the PCA regimen were totalled. The mean 4-hourly totals for patients in the three groups are shown in figure 1. There were no significant differences between the scores of the three groups during any of these periods.

Table II shows the numbers of patients in each group who were receiving PCA at the end of each 12-h period after operation.

Sp_{O_2} readings were accepted as valid and recorded only if they were consistent over 2–3 min and there was a good pulse signal on the oximeter screen. The occurrence of hypoxaemic episodes (defined as $Sp_{O_2} < 94\%$) in the three groups is shown in table III. Group B10 had significantly more recordings less than 94% compared with groups B0 ($P < 0.001$) and B4 ($P < 0.001$). Group B0 had significantly more recordings less than 94% compared with group B4 ($P < 0.01$). The smallest Sp_{O_2} values in the three groups were 86–95% (mean 91.6%) in group B0, 86–95% (mean 92.4%) in group B4 and 86–95% (mean 90.3%) in group B10.

The slowest ventilatory frequencies recorded in the three groups were 12–18 b.p.m. in group B0, 12–20 b.p.m. in group B4 and 14–18 b.p.m. in group B10.

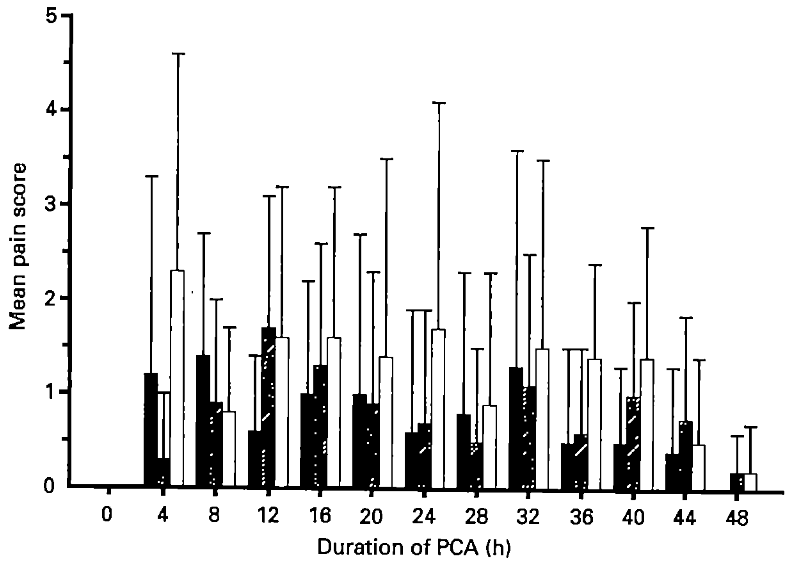

FIG. 1. Mean (SD) 4-hourly total pain scores in groups B0 (■), B4 (▨) and B10 (□).

TABLE II. *Numbers of patients in each group using PCA after each 12-h interval after operation*

	Group B0	Group B4	Group B10
12 h	15	15	15
24 h	15	15	15
36 h	13	13	14
48 h	2	4	3

TABLE III. *Comparison of incidence of Sp_{O_2} readings less than 94% in the three groups. **Significantly greater than group B4 ($P < 0.01$, $\chi^2 = 6.9$); ***significantly greater than B0 and B4 ($P < 0.001$, $\chi^2 = 51$)*

	Group B0	Group B4	Group B10
$Sp_{O_2} < 94\%$	78**	56	159***
$Sp_{O_2} \geq 94\%$	499	583	523

TABLE IV. *Comparison of the incidence of emetic sequelae in the three groups. ***Significant difference ($P < 0.001$) compared with groups B0 ($\chi^2 = 16.2$) and B4 ($\chi^2 = 14.9$)*

	Group B0	Group B4	Group B10
Episodes of emetic sequelae	20	22	60***
No. of patients who complained of emetic sequelae	8	8	10

TABLE V. *Comparison of duration of sleep between 22:00 and 06:00 (night) and between 06:00 and 22:00 (day) in the three groups. *Significant difference ($P < 0.05$) compared with groups B4 ($\chi^2 = 5.3$) and B10 ($\chi^2 = 5.3$)*

	Group B0	Group B4	Group B10
Night			
Asleep	142*	178	217
Awake	78	61	68
Day			
Asleep	85	92	86
Awake	272	308	311

A sedation score of 3 was not recorded in any patient. A sedation score of 2 occurred on 22 occasions in group B0, 19 in group B4 and on 21 occasions in group B10 (not significant).

Group B10 suffered significantly more emetic sequelae than groups B0 ($P < 0.001$) and B4 ($P < 0.001$) (table IV). There was no significant difference in the incidence of emetic sequelae between groups B0 and B4. Antiemetics were given to one patient in group B10.

The amount of time spent asleep was compared in the three groups by analysing the periods from 22:00 (after the evening ward drug round) to 06:00 (night) and from 06:00 to 22:00 (day) separately. Groups B4 and B10 spent significantly more time asleep at night compared with patients in group B0 ($P < 0.05$). There was no significant difference between groups B4 and B10 in the amount of time spent asleep at night, and no significant differences between the groups in the amount of time spent asleep during the day (table V). Similar numbers of patients in all groups were operated upon during the day and at night.

Three patients in group B10 had the background infusion discontinued because of persistent excessive sedation.

DISCUSSION

There are few controlled studies which have compared different PCA regimens for children in terms of efficacy, dosage and adverse effects. The role for a background infusion with PCA has not been defined clearly. The perceived advantage of using a background infusion is that it improves continuity of analgesia and provides analgesia during sleep. This may improve sleep patterns in postoperative patients by reducing the number of occasions when patients are wakened by pain which requires subsequent use of the PCA device for relief.

The operation of appendicectomy provides a good model for the study of postoperative analgesic regimens. It involves a standard surgical procedure and a degree of peritoneal irritation which ensures that postoperative morphine requirements when self-administered with a PCA machine are of the order of 20–30 μg kg^{-1} h^{-1}, which is the same as that in children after more major abdominal and orthopaedic surgery [11–14].

This study has shown that the use of a background infusion of morphine 4 μg kg^{-1} h^{-1} in a PCA regimen for children after lower abdominal surgery caused no increase in side effects compared with no background infusion and was associated with less hypoxaemia and a better sleep pattern than PCA only. A background infusion of morphine 10 μg kg^{-1} h^{-1} was associated with a better sleep pattern also, but was accompanied by a significant increase in the incidence of hypoxaemia and nausea and vomiting. Unlike a background infusion of 20 μg kg^{-1} h^{-1} [8], these smaller infusion rates were not associated with an increase in the incidence of excess sedation.

The reason why a background infusion of morphine 4 μg kg^{-1} h^{-1} produces less hypoxaemia than a PCA regimen with no background infusion may be that the infusion produced better analgesia and improved ventilation. This suggests that the method for assessing pain used in this study (patient self-report) is relatively insensitive. A specific assessment of pain on moving or coughing may have revealed differences in analgesia between groups B0, B4 and B10. We have also previously noted that periods of hypoxaemia often correspond with high pain scores [9].

In adult studies, the use of a background infusion has been shown to improve pain relief in two studies [2, 3], but not in others [4–6]. The studies which found no benefit from a background infusion did not assess pain during movement. In contrast, one of the studies which did find improved analgesia with a background infusion [3] did assess pain on movement. The other study [2] did not make clear if pain was assessed only at rest or during movement. Two studies [3, 5] found an increase in opioid-induced side effects (other than respiratory depression) with a background infusion. The size of background infusion of morphine varied from 0.6 mg h^{-1} to 1.5 mg h^{-1} (pethidine 10 mg h^{-1} in one), which is equivalent to 10–20 μg kg^{-1} h^{-1}.

In paediatric practice, two studies [7, 8] have compared PCA with and without a background infusion. In one [7] the infusion used was morphine 15 μg kg^{-1} h^{-1} and there were no differences in morphine consumption, sedation, nausea or vomiting. Respiratory depression (as measured by ventilatory frequency) was not noted in any patient. The PCA plus background infusion group were found to have smaller pain scores than the PCA only group as assessed by patient and nurse visual analogue scales.

In the other study [8], a background infusion of morphine 20 μg.kg^{-1} h^{-1} produced a significant increase in morphine consumption without improving pain scores (assessed by patient self-report). There was also a significant increase in the incidence of opioid-induced side effects (respiratory depression, excessive sedation, nausea and vomiting) in the background infusion group. However, the use of a background infusion was associated with a better sleep pattern.

Opioid-induced respiratory depression has been considered to be a risk of background infusion, but has been shown to occur only in one paediatric study [8] when Sp_{O_2} was measured continuously with patients breathing air. Intermittent recording of ventilatory frequency has been shown to be an insensitive monitor of opioid-induced respiratory depression in adults [15–17]. Studies which have relied on intermittent recording of ventilator frequency as an indicator of respiratory depression and have concluded that a background infusion does not produce respiratory depression [2–7] may be falsely optimistic. Arterial oxygen saturation while breathing air is a more sensitive monitor of adequate ventilation. Sp_{O_2} 94% corresponds to an arterial oxygen tension of 10 kPa and indicates mild hypoxaemia. In the absence of other causes of hypoxaemia, this indicates a degree of ventilatory depression which may be caused by opioid administration or pain. In our experience, pain is a more common reason for hypoxaemia than opioid overdosage. This emphasizes the need for careful and repeated assessments by experienced staff.

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PHARMACOKINETICS OF I.V. AND RECTAL PETHIDINE IN CHILDREN UNDERGOING OPHTHALMIC SURGERY

K. HAMUNEN, E.-L. MAUNUKSELA, T. SEPPÄLÄ AND K. T. OLKKOLA

SUMMARY

We have studied the pharmacokinetics of i.v. and rectal pethidine in 20 children age 4–8 yr undergoing ophthalmic surgery. After i.v. administration, the clearance of pethidine was mean 10.4 (SD 1.7) ml kg^{-1} min^{-1}, volume of distribution at steady state 2.8 (0.6) litre kg^{-1} and elimination half-life 3.0 (0.5) h. After rectal administration, plasma pethidine concentrations varied greatly and peak concentrations appeared late, at 147 (44) min. The mean systemic bioavailability after rectal administration was approximately 55%. Because the bioavailability of rectal pethidine varies greatly, this route is not encouraged in the management of acute pain. (Br. J. Anaesth. 1993; **71**: 823–826)

KEY WORDS

Pharmacokinetics. Analgesics, opioid: pethidine. Children.

Pethidine is often used in paediatric premedication and pain management. It may be administered parenterally or enterally and in premedication it has also been used in combination with promethazine and chlorpromazine [1]. Pethidine is metabolized in the liver by hydrolysis and N-demethylation; both reactions are known to be age-dependent [2, 3]. In neonates, the elimination half-life of pethidine is seven times greater than that in adults [4]. However, there are only limited data on the pharmacokinetics of pethidine in older children. Jacobsen and colleagues studied the pharmacokinetics of i.v., i.m. and rectal pethidine in children aged 7–13 yr [5]. Unfortunately, the short blood sampling period did not allow determination of pharmacokinetic parameters.

The objective of this study was to investigate the pharmacokinetics of i.v. and rectal pethidine in children. The concentrations of pethidine were measured for 8–14 h after administration and their relationships with duration of analgesia, onset of spontaneous breathing and end-tidal carbon dioxide concentrations were determined.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and parental informed consent obtained. We studied 20 healthy children (ASA I–II) aged 4–8 yr undergoing elective ophthalmic surgery. Patients were allocated randomly to two groups of 10: i.v. and rectal (suppository).

Premedication comprised oral liquid flunitrazepam 0.1 mg kg^{-1} (maximum 2 mg). I.v. infusion of 5% glucose in 0.3% normal saline was started at a rate of 10 ml kg^{-1} h^{-1} for the first 1 h and then 2.5 ml kg^{-1} h^{-1} until the end of the study. Anaesthesia was induced with thiopentone 5 mg kg^{-1}. The trachea was intubated and the lungs ventilated using a Servo 900 ventilator (Siemens, Sweden). Anaesthesia was maintained with 70% nitrous oxide and 1–2 vol% halothane in oxygen. Relaxation was produced with pancuronium and the degree of the block was monitored using a transcutaneous nerve stimulator. At the end of anaesthesia, residual neuromuscular block was antagonized with neostigmine and glycopyrronium.

After induction of anaesthesia, pethidine hydrochloride (Petidin, Leiras, Finland) 1 mg kg^{-1} was injected via a venous cannula in a foot for the 10 patients in the i.v. group. At 2, 5, 10, 15, 30, 60, 120, 180, 240 min and 6–8 h after administration of pethidine, blood samples (2 ml) were obtained from a cannula inserted in a hand vein. Similarly, after induction of anaesthesia, patients in the rectal administration group were given a pethidine suppository of pethidine hydrochloride 100 mg in a solid fat base (Petidin, Leiras, Finland). Blood samples were collected at 15, 30, 45, 60, 90, 120, 180, 240 min, 6–8 h and 14–18 h after administration of the suppository. In addition, a venous blood sample was collected when postoperative pain was noted. A total of 20–24 ml of blood (less than 2% of the patient's blood volume) was obtained in both groups. Plasma was separated and stored at −20 °C until subsequent analysis. No other analgesics were given during anaesthesia. There was no blood loss during or after the operation.

During anaesthesia, topical anaesthetic cream (EMLA, Astra, Sweden) was applied to the patient's nostrils to facilitate end-tidal gas measurement. At the end of anaesthesia, the nose was cleared by suction and a small plastic tube for end-tidal gas sample collection was placed in one nostril. End-tidal carbon dioxide (E'_{CO_2}) and halothane concen-

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trations were recorded using a Capnomac (Datex, Finland). After operation, pain was assessed by the patient and by a trained observer according to a scale in routine use in the department and described earlier by Maunuksela, Olkkola and Korpela [6]. If the patient was noted to have pain, i.v. diclofenac 1 mg kg^{-1} was given as clinically indicated, as rescue analgesic. All side effects and adverse reactions were recorded.

Pethidine was assayed by a gas chromatographic method modified from a method developed to determine pentazocine and codeine [7]. A sample of 0.5 ml was buffered with 1 ml of Na_2HPO_4 0.5 mol $litre^{-1}$ (pH 8.5) and extracted with 5 ml of a N-hexane–dichlormethane mixture (70:30) containing flurazepam 80 ng ml^{-1} as internal standard. After centrifugation, the aqueous phase was removed and the organic layer evaporated to dryness. The residue was then dissolved with ethanol 100 µl and 2 µl of solution was injected onto a Hewlett–Packard 5880 gas chromatograph equipped with a 25 m × 0.31 mm phenyl-methyl silicone SE-54-capillary column (film thickness 0.17 µm) and Hewlett–Packard nitrogen–phosphorus detector. The carrier gas was helium (flow rate 2–3 ml min^{-1}). The oven temperature was changed from 200 to 300 °C at a rate of 15 °C min^{-1} and held constant at 300 °C thereafter. Retention times for pethidine and flurazepam were 4.02 and 10.3 min, respectively. Limit of detection was 5 ng ml^{-1} for pethidine; within-day variation, expressed as the coefficient of variation for successive pooled plasma aliquots was 4.8 % with pethidine 290 ng ml^{-1} ($n = 9$) and 7.5 % with pethidine 53 ng ml^{-1} ($n = 8$). Checks were made to ensure that opioids, NSAID, paracetamol and a variety of the CNS active drugs did not interfere with the assay of pethidine.

In the i.v. group, pethidine concentrations at the occurrence of pain were obtained from the same sample drawn at that time in four patients (Nos 2, 3, 8, 9) and for six patients the concentrations were estimated using the fitted multiexponential function. For all patients in the i.v. group, pethidine concentrations at the onset of spontaneous breathing were estimated using the fitted multiexponential function. In the rectal group, corresponding concentrations were estimated using linear interpolation.

Pharmacokinetic analysis

I.v. administration of pethidine. Individual plasma concentrations were fitted to the following multiexponential function with the aid of a microcomputer-based non-linear regression program [8]:

$$C = \sum_{i=1}^{n} A_i e^{-a_i t}$$

where C = plasma concentration of pethidine at time t; A_i = a zero-time intercept; a_i = a disposition rate constant. The measured concentration values were weighted with equal weights and with the factor $1/C^2$. Goodness of fit was determined by Akaike's information criterion [9] and by assessment of randomness of scatter of data points about the fitted function. The initial estimates were obtained using an iterative curve-stripping technique [10]. The pharmacokinetic parameters, elimination half-life ($T_{\frac{1}{2}}$), area under the pethidine concentration–time curve ($AUC_{0-\infty}$), volume of the central compartment (V_c), steady state volume of distribution (V^{ss}) and clearance (Cl) were calculated according to standard formulae [11].

Rectal administration of pethidine. Peak pethidine concentrations (Cmax), concentration peak times (tCmax) and $AUC_{0-\infty}$ were calculated for each subject. $AUC_{0-\infty}$ was calculated using the linear trapezoidal rule while successive concentration values were increasing, and the logarithmic trapezoidal rule when successive concentration values were decreasing after the peak concentration. $AUC_{0-\infty}$ was extrapolated to infinity using the respective elimination rate constant, which was calculated by regression analysis of the log-linear part of the curve. For calculation of kinetic parameters, linear kinetics were assumed [12].

RESULTS

Characteristics of the patients and pharmacokinetic parameters in the i.v. group are shown in table I. The plasma concentrations of pethidine were described by a tri-exponential function in patients Nos 1, 2 and 7 and by a bi-exponential function in the others. Weighting with the factor $1/C^2$ resulted in a better fit than weighting with equal weights. Mean elimination half-life was 3.0 (SD 0.5) h and clearance was 10.4 (1.7) ml kg^{-1} min^{-1}. V_c and V^{ss} values were 1.0 (0.3) litre kg^{-1} and 2.8 (0.6) litre kg^{-1}, respectively.

Characteristics of the patients and pharmacokinetic parameters in the suppository group are shown in table II. The percent extrapolated area beyond the observation was 15 (9) % after rectal administration of pethidine and 15 (6) % after i.v. administration. After rectal administration of pethidine, Cmax values were in the range 88–1050 ng ml^{-1}. The estimated systemic bioavailability after rectal administration of pethidine was 55 %. Correlation between dose calculated per body weight and Cmax was not statistically significant ($P < 0.06$). The time courses of plasma pethidine concentrations after i.v. and rectal administration are shown in figures 1 and 2, respectively.

Onset of spontaneous breathing occurred at 5.3 (2.7) min and 6.4 (2.1) min after discontinuation of anaesthesia in the i.v. and suppository groups, respectively. At the onset of spontaneous breathing, pethidine concentration in the i.v. group was 255 (52) ng ml^{-1} (range 158–304 ng ml^{-1}). The corresponding E'_{CO_2} and end-tidal halothane concentrations were 9.6 (0.4) % and 0.6 (0.1 %), respectively. In the suppository group, the respective values for pethidine, E'_{CO_2} and halothane concentrations were 227 (100) ng ml^{-1} (range 32–622 ng ml^{-1}), 9.0 (1.0) % and 0.5 (0.1) %. There was no linear correlation between pethidine concentrations and E'_{CO_2} values at the onset of spontaneous breathing in either group.

Duration of sleep after operation was 94 (15) min

TABLE I. *Patient characteristics and pharmacokinetic parameters of pethidine after an i.v. injection of pethidine 1 mg kg⁻¹*

Patient No.	Age (yr)	Weight (kg)	Height (cm)	Duration of surgery (min)	$AUC_{0-\infty}$ (ng min ml⁻¹)	*Cl* (ml kg⁻¹ min⁻¹)	$T_{\frac{1}{2}}$ (h)	V_c (litre kg⁻¹)	V^{ss} (litre kg⁻¹)
1	6.8	22.0	115.5	40	68400	12.7	3.3	1.1	3.0
2	6.1	20.0	114.5	53	104700	8.4	2.8	0.3	4.1
3	6.0	21.5	117.5	35	83100	10.4	2.5	0.9	2.1
4	5.5	25.0	117.0	45	99800	8.7	4.1	1.0	3.0
5	4.9	20.5	112.0	58	90600	9.6	2.8	1.0	2.3
6	5.3	16.0	106.0	82	71900	12.1	3.0	1.1	2.9
7	4.2	17.0	107.0	42	85000	10.3	3.4	1.1	2.5
8	6.6	21.0	120.0	61	64100	13.6	2.6	1.1	2.9
9	5.3	17.5	107.0	33	86600	10.1	2.7	0.9	2.3
10	7.0	26.0	130.0	72	97100	9.0	3.3	1.0	2.5
Mean	5.5	20.7	114.7	52	85100	10.4	3.0	1.0	2.8
SD		3.3	7.3	16	13600	1.7	0.5	0.3	0.6

TABLE II. *Patient characteristics and pharmacokinetic parameters of pethidine after rectal administration of pethidine 100 mg. AUC values are standardized for a dose of pethidine 1 mg kg⁻¹*

Patient No.	Age (yr)	Weight (kg)	Height (cm)	Duration of surgery (min)	Dose (mg kg⁻¹)	$AUC_{0-\infty}$ (ng min ml⁻¹)	*C*max (ng ml⁻¹)	*tC*max (min)	$T_{\frac{1}{2}}$ (h)
1	6.3	22.0	118.0	40	4.5	70700	1050	90	4.8
2	8.3	24.0	123.5	52	4.2	55200	471	180	4.5
3	5.3	19.5	110.0	35	5.1	45100	640	120	3.5
4	6.7	20.5	120.0	31	4.9	37600	362	120	3.7
5	8.6	28.0	134.5	75	3.6	47900	457	120	3.4
6	8.8	30.0	134.5	35	3.3	20400	88	180	8.8
7	7.7	33.0	136.5	38	3.0	41300	247	120	4.9
8	7.7	28.0	131.0	33	3.6	48000	467	120	4.0
9	6.9	29.0	126.5	45	3.4	45400	289	180	5.1
10	8.9	27.0	130.0	27	3.7	54400	270	242	7.1
Mean	7.5	26.1	126.5	41	3.9	46600	434	147	5.0
SD		4.2	8.1	13	0.7	13000	251	44	1.7

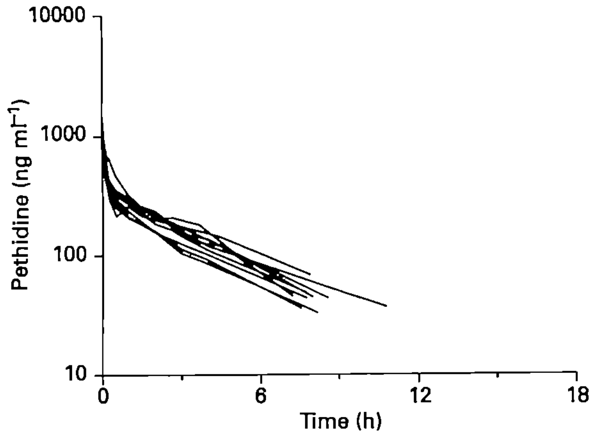

FIG. 1. Pethidine plasma concentrations after i.v. administration of pethidine 1 mg kg⁻¹ during ophthalmic surgery in 10 children.

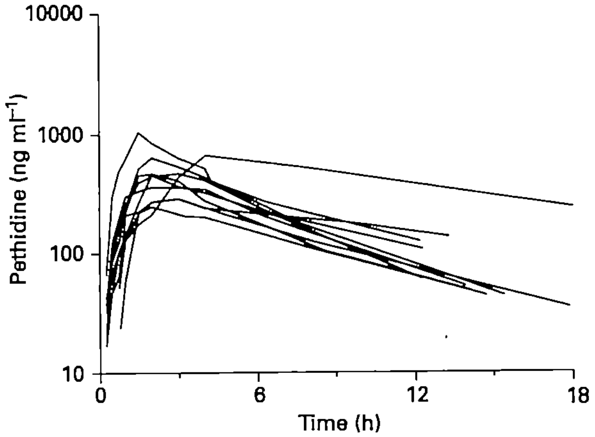

FIG. 2. Pethidine plasma concentrations after rectal administrations of pethidine 100 mg during ophthalmic surgery in 10 children.

and 130 (15) min in the i.v. and suppository groups, respectively. Nine patients in the i.v. group and six in the rectal group experienced pain during the day of operation. Time to occurrence of pain after pethidine administration and pethidine concentration at occurrence of pain were 208 (35) min and 146 (33) ng ml⁻¹ in the i.v. group and 259 (66) min and 196 (80) ng ml⁻¹ in the suppository group.

The incidence of nausea was four patients in each group. One patient in the i.v. group did not urinate during the day of operation. Shortly after the injection of pethidine, histamine release reaction along the vein was observed in two patients. Sixty minutes after administration of pethidine suppository, a 6.3-yr-old boy developed transient bigeminy with an E'_{CO_2} value exceeding 10%. He did not have any known heart disease. No action was taken and bigeminy disappeared as E'_{CO_2} decreased.

DISCUSSION

Drug metabolism appears to be dependent on the age of the patient. For most drugs, the rate of metabolism, when expressed per body weight, is slower in neonates than in adults, but it normally reaches and even exceeds adult values within the first year of life. Although some children may be able to eliminate drugs rapidly, there are great individual differences, especially at young age [2, 3]. The pharmacokinetics of pethidine have been extensively studied in adults [12–16], but in paediatric age groups there are data only on newborn babies and only one study with limited follow-up time in older children [4, 5]. In our study, the mean pharmacokinetic parameters, clearance, volume of distribution and elimination half-life were the same as observed earlier in adults [12, 14–16]. Our study was performed during operation and the early postoperative period. In adults pethidine clearance appears to be less during operation than during the late postoperative period and in volunteers [15]. If this is applicable also to children, even greater clearance values would be obtained during the late postoperative period or in healthy children not undergoing surgery. The longer terminal half-life in the suppository group was probably caused by the slow release from the suppository.

The route of administration of a drug is important in the management of pain in children. Rectal administration avoids painful i.m. injections; it is an alternative to oral administration in the presence of nausea and vomiting and might decrease first-pass elimination of high-clearance drugs such as opioids [17]. In contrast, plasma drug concentrations after rectal administration may vary unpredictably, as demonstrated by the widely varying pethidine concentrations in this study. The greatest peak concentration was more than 10 times greater than the smallest. Large individual variability in blood pethidine concentrations after rectal administration of pethidine has been noted previously [5]. Possible explanations for this include factors affecting rectal absorption of a drug and the route of venous drainage of the rectum [17]. However, in our study these factors could not be controlled. Hepatic drug metabolism is affected by anaesthesia [18]. In the present study, the depth of anaesthesia was the same in all patients, but the durations of surgery varied. Because peak concentrations and concomitant pain relief and potential adverse effects are delayed after rectal administration, this route of administration of pethidine cannot be considered safe and is not recommended for the management of acute pain. The time to peak concentration for rectal pethidine in the present study (147 min) was shorter than that (180 min) reported earlier in children. In contrast, the systemic bioavailability of rectal pethidine estimated by comparing the $AUC_{0-\infty}$ values obtained from the i.v. and rectal groups was slightly greater than that reported previously in children [5].

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INFLUENCE OF CROHN'S DISEASE ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF ALFENTANIL

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SUMMARY

We have compared the dose requirements, pharmacokinetics and pharmacodynamics of alfentanil in 12 patients with Crohn's disease and 10 control patients undergoing abdominal surgery. Plasma concentrations of α_1-acid glycoprotein (AAG) and alfentanil protein binding were also measured. Anaesthesia was induced with alfentanil 100 $\mu g\ kg^{-1}$ and thiopentone, and maintained with nitrous oxide in oxygen and alfentanil 25–200 $\mu g\ kg^{-1}\ h^{-1}$. Arterial blood samples were obtained before and after each change in the alfentanil infusion rate and for 6 h after stopping the infusion. Pharmacokinetic data were derived using non-compartmental methods. Alfentanil concentration–effect data were evaluated by non-linear regression, where effect was either response or no response to surgical stimulation. Mean intra-operative alfentanil requirement was greater in patients with Crohn's disease (2.48 $\mu g\ kg^{-1}\ min^{-1}$) than in control patients (1.35 $\mu g\ kg^{-1}\ min^{-1}$) ($P < 0.01$*). Mean elimination half-life, total plasma clearance and steady state distribution volume in patients with Crohn's disease were comparable to those in control patients (80* vs *81 min, 5.7* vs *6.4 ml $kg^{-1}\ min^{-1}$ and 0.70* vs *0.68 litre kg^{-1}, respectively). Mean plasma concentration at which the probability of no response was 50% for the intra-abdominal period of surgery was greater in the Crohn group (359 ng ml^{-1}) than in the control group (199 ng ml^{-1}) (*$P < 0.02$*). Plasma AAG concentrations were greater in the Crohn group, but the free fraction of alfentanil was similar in both groups. This study indicates that the increased alfentanil requirement in patients with Crohn's disease may be attributed to a change in pharmacodynamics.* (Br. J. Anaesth. 1993; **71**: 827–834)

KEY WORDS

Analgesics: alfentanil. Anaesthetics, intravenous: alfentanil. Pharmacokinetics: alfentanil. Pharmacodynamics: alfentanil, plasma protein binding.

The dose requirement of alfentanil, given as a supplement to patients receiving nitrous oxide anaesthesia during abdominal surgery, is increased in patients with Crohn's disease [1]. It is not known if this increased requirement is caused by altered pharmacokinetics, altered pharmacodynamics, or both. A factor that may be of importance in this respect is protein binding. Alfentanil binds in plasma mainly to α_1-acid glycoprotein (AAG) [2]. Various disease states, including Crohn's disease, are associated with an increased plasma AAG concentration and this may influence the binding of drugs [3]. However, alfentanil binding varies considerably between patients and is not necessarily increased in all disease states associated with increased plasma concentrations of AAG [4].

This study was designed to see if the altered dose–effect relationship in patients with Crohn's disease is related to changes in the pharmacokinetics or in the pharmacodynamics of alfentanil. Furthermore, in order to ascertain if Crohn's disease influences the plasma protein binding of alfentanil, we have determined also the protein binding in these patients and compared the data with those obtained in control patients.

PATIENTS AND METHODS

We studied 22 patients, aged 20–55 yr, ASA I or II, during elective abdominal surgery. The study was approved by the Committee on Medical Ethics of the University of Leiden and informed consent was obtained from all patients. Twelve patients had histologically or radiologically proven Crohn's disease. The severity of the inflammatory process in these patients was assessed before operation according to the Modified Activity Index (MAI) [5]. Ten other patients without Crohn's disease served as a control group. Patients with diseases, other than Crohn's disease, known to be associated with increased or decreased plasma concentrations of AAG [6] were excluded, as were patients with clinical or biochemical evidence of renal or hepatic dysfunction or a history of alcohol abuse. Patients taking opioids on a regular basis were also excluded.

Midazolam 0.1 mg kg^{-1} i.m. was given 30 min before induction of anaesthesia. Before induction a

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cannula was inserted in a radial artery for continuous arterial pressure monitoring and collection of blood samples. Pancuronium 0.02 mg kg^{-1} was given to reduce the risk of muscle rigidity and patients were allowed to breathe 100% oxygen for 2 min. Anaesthesia was induced with alfentanil 100 μg kg^{-1} administered over 30 s, supplemented with thiopentone as necessary until consciousness was lost. Suxamethonium 1 mg kg^{-1} was given to facilitate intubation of the trachea. Immediately after administration of the initial dose of alfentanil, a continuous infusion of alfentanil was started at 50 μg kg^{-1} h^{-1}.

An additional dose of pancuronium 0.04 mg kg^{-1} was given after intubation and the patient's lungs were ventilated with 66% nitrous oxide in oxygen. Ventilation was adjusted to maintain the end-tidal carbon dioxide partial pressure (recorded with a Datascope 500 CO_2 analyser) at 4–4.5 kPa for the entire operation. Only minimal additional doses of pancuronium, as necessary for surgery, were given so that somatic responses could be identified. The electrocardiogram and arterial pressure were displayed continuously.

An internal jugular vein was cannulated for measurement of central venous pressure. Nasopharyngeal temperature, urine production and blood loss were recorded every 15 min. Fluid losses were replaced by saline or whole blood, as indicated, to maintain adequate urine output and central venous pressure of 8–10 mm Hg.

The infusion rate of alfentanil was adjusted to maintain adequate anaesthesia. The occurrence of one of the following responses to surgical stimuli was taken as an indication of inadequate anaesthesia:

(1) An increase in systolic arterial pressure or heart rate to more than 20% greater than "normal" (defined as the average of three measurements made on the evening before surgery, on the morning of surgery before premedication and just before induction of anaesthesia).

(2) Other autonomic signs of inadequate anaesthesia such as lachrymation, flushing or sweating.

(3) Somatic responses (swallowing, coughing, eye opening or body movements).

If a response occurred, alfentanil 10 μg kg^{-1} was given as a bolus and the infusion rate was increased by 25 μg kg^{-1} h^{-1} to a maximum rate of 200 μg kg^{-1} h^{-1}. If a patient did not respond during a 15-min period, the alfentanil infusion rate was decreased by 25 μg kg^{-1} h^{-1} to a minimum of 25 μg kg^{-1} h^{-1}.

During the study, every patient was monitored by two observers: an anaesthetist in training and a staff anaesthetist. Both persons were familiar with the definition of inadequate anaesthesia as used in this study, and looked continuously for clinical responses. If a response was detected, it was accepted only if verified by both observers. All the operations were performed by the same surgeon.

The alfentanil infusion was discontinued 10 min before the anticipated end of surgery and nitrous oxide administration was stopped at the end of the operation. Residual neuromuscular block was antagonized with a mixture of atropine 0.5 mg and neostigmine 1 mg. The trachea was extubated when ventilation was adequate, without stimulation (defined as tidal volume greater than 7 ml kg^{-1}, ventilatory frequency greater than 10 b.p.m. and end-tidal carbon dioxide partial pressure less than 6.5 kPa). If a patient did not regain adequate ventilation within 10 min after discontinuation of nitrous oxide, naloxone 0.04 mg was administered i.v. every 1–2 min until adequate spontaneous ventilation was established.

Blood samples and assays

Arterial blood samples were obtained for measurement of plasma alfentanil concentrations in heparinized syringes before and 2, 7 and 15 min after the alfentanil infusion was started and every 30 min thereafter. Samples were obtained also at the occurrence of a response and 2, 7 and 15 min after subsequent alfentanil bolus administration. Additional samples were obtained just before and 3, 6, 10, 15, 30, 60, 120, 180, 240, 300 and 360 min after the alfentanil infusion was stopped, and at extubation of the trachea. Additional arterial blood samples were obtained 15 min after induction and at the time of extubation for measurement of plasma concentrations of AAG and the degree of protein binding of alfentanil. Plasma was separated by centrifugation and stored at −20 °C until required for assay. Plasma concentrations of AAG were measured by rate nephelometry using the Array Protein System (Beckmann) [7]. The plasma protein binding of alfentanil was assessed by equilibrium dialysis, as described elsewhere [8]. Alfentanil concentrations were measured by capillary gas–liquid chromatography [8]. The coefficients of variation in the concentration ranges encountered in this study were < 5% for both AAG and alfentanil.

Data analysis

The average alfentanil dose requirement (μg kg^{-1} min^{-1}) (excluding the initial bolus dose) was calculated for each patient. Elimination half-lives were calculated by linear regression analysis of the log-linear terminal part of the plasma concentration–time curves. Total plasma clearances and volumes of distribution at steady state were derived using non-compartmental analysis [9].

For each patient, the state of responsiveness (presence or absence of a clinical response to surgical stimuli) during the intra-abdominal period of the operation was related to the corresponding plasma concentrations by the following version of the Hill equation:

$$\text{probability of no response} = \frac{C_P^{\gamma}}{C_{P,50}^{\gamma} + C_P^{\gamma}}$$

where C_P = measured plasma alfentanil concentration; $C_{P,50}$ = plasma concentration at which the probability of no response is 50%; γ = a dimensionless parameter characterizing the slope of the concentration–response curve. The equation was fitted to the data by unweighted least-squares, non-linear regression analysis with the software package Siphar (Simed, Creteil, France).

Data are presented as mean (SD) unless specified

TABLE I. *Patient data: control patients. †Median (range). Ch. = Cholecystectomy; SBR = small bowel resection; A = adhesiotomy; S = sigmoidectomy. *Compared with patients with Crohn's disease (see table II); ns = not significant*

Patient No.	Age (yr)	Weight (kg)	Sex (F/M)	Surgery	Duration of infusion (min)	Blood loss (ml)
1	55	88	F	Ch.	120	250
2	48	50	F	SBR	257	1500
3	28	95	M	SBR	181	1400
4	34	52	F	A	62	100
5	54	53	F	A	70	70
6	39	93	M	S	324	1000
7	54	84	M	S	150	700
8	20	85	M	SBR	138	100
9	43	85	F	Ch.	135	300
10	45	63	F	SBR	201	500
Mean	42	75			164	400†
SD		18			81	70–1500†
P*	ns	< 0.05	ns		ns	ns

otherwise. Linear regression was used to assess possible relationships between the average alfentanil dose requirement and the duration of the alfentanil infusion within each group and to examine possible relationships between MAI and $C_{P,50}$, AAG concentrations and dose requirements. The two-sample *t* test or the Mann–Whitney *U* test was used for intergroup comparisons, as appropriate. Plasma concentrations of AAG and the degree of protein binding in the samples obtained 15 min after induction and at the time of extubation were compared using paired *t* tests. $P < 0.05$ was considered statistically significant.

RESULTS

The two groups of patients were comparable with respect to age, sex, duration of alfentanil infusion and blood loss, but the mean body weight was less in the group of patients with Crohn's disease than in the control group ($P < 0.05$) (tables I, II). Table II also shows the MAI score, as a measure of activity of the inflammatory bowel disease for the patients with Crohn's disease. Eleven of the 12 patients with Crohn's disease were receiving salazosulphapyridine or mesalazine medication before operation, one patient received azathioprine and nine patients were

TABLE II. *Patient data: patients with Crohn's disease. †Median (range). SBR = Small bowel resection; IR = ileocecal resection; C = colectomy; MAI = modified activity index (an index of the severity of Crohn's disease). * Compared with control patients (table I); ns = not significant*

Patient No.	Age (yr)	Weight (kg)	Sex (F/M)	Surgery	Duration of infusion (min)	Blood loss (ml)	MAI
1	28	53	F	SBR	149	100	99
2	42	54	F	IR	108	350	144
3	26	70	F	C	213	1700	157
4	21	62	F	IR	172	300	121
5	31	63	F	IR	212	600	138
6	37	50	F	IR	153	800	138
7	38	70	F	C	262	1300	132
8	40	65	F	C	164	800	129
9	29	61	F	IR	140	200	137
10	39	72	M	C	175	300	136
11	26	53	F	SBR	298	1200	179
12	56	53	F	SBR	164	750	133
Mean	34	61			184	675†	137
SD		8			54	100–1700†	19
P*	ns	< 0.05	ns		ns	ns	ns

TABLE III. *Alfentanil requirement, plasma concentrations of AAG and unbound percentages of alfentanil in control patients. AAG = α_1-Acid glycoprotein. * Compared with patients with Crohn's disease (table IV); ns = not significant*

Patient No.	Alfentanil requirement (μg kg^{-1} min^{-1})	AAG concn (g litre^{-1})		Unbound alfentanil (%)	
		15 min after induction	At extubation	15 min after induction	At extubation
1	0.65	0.37	0.40	—	—
2	2.57	0.55	0.33	8.9	11.7
3	0.90	0.49	0.36	9.3	11.6
4	1.62	0.32	0.34	12.2	13.7
5	1.78	0.42	0.38	14.6	—
6	1.10	0.59	0.59	14.5	14.2
7	2.21	0.42	0.38	13.6	11.6
8	0.85	0.84	0.86	7.4	7.1
9	0.79	0.50	0.52	6.9	6.7
10	1.11	0.79	0.60	—	—
Mean	1.35	0.53	0.48	10.9	10.9
SD	0.66	0.17	0.17	3.2	3.0
P*	< 0.01	< 0.02	ns	ns	ns

TABLE IV. *Alfentanil requirement, plasma concentrations of AAG and unbound percentages of alfentanil in patients with Crohn's disease. AAG = α_1-Acid glycoprotein.* * *Compared with control patients (table III); ns = not significant;* *** *P < 0.001 compared with values 15 min after induction.* † *P < 0.05 compared with values 15 min after induction*

Patient No.	Alfentanil requirement (μg kg^{-1} min^{-1})	AAG concn (g litre^{-1}) 15 min after induction	AAG concn (g litre^{-1}) At extubation	Unbound alfentanil (%) 15 min after induction	Unbound alfentanil (%) At extubation
1	1.06	0.45	0.33	15.4	20.5
2	2.37	0.51	0.49	13.0	12.3
3	4.52	1.30	0.83	4.9	5.3
4	1.04	0.50	0.44	3.8	7.6
5	2.37	0.67	0.52	9.1	10.3
6	3.06	0.75	0.59	10.8	14.5
7	3.75	1.11	0.81	10.8	17.9
8	2.89	0.99	0.70	13.3	18.5
9	1.54	1.34	1.19	8.1	7.3
10	1.92	0.71	0.64	11.2	12.9
11	2.20	1.72	1.25	5.7	5.8
12	3.00	0.56	0.44	17.2	—
Mean	2.48	0.88	0.69***	10.3	12.1†
SD	1.04	0.41	0.29	4.2	5.3
*P**	< 0.01	< 0.02	ns	ns	ns

receiving corticosteroids. In the control group, only one patient (No. 9) received medication, consisting of metoclopramide and an antacid preparation.

The loading dose of alfentanil 100 μg kg^{-1} alone was not sufficient to induce anaesthesia and had to be supplemented with increments of thiopentone until consciousness was lost. Median thiopentone dose in both groups was 3 mg kg^{-1} (range 2–4 mg kg^{-1}). There was no significant difference in supplementary thiopentone dose between the groups.

Tables III and IV show the alfentanil dose requirements, plasma AAG concentrations and percentage of free alfentanil at 15 min after induction and at extubation in both groups. Within each group, alfentanil requirements were independent of the duration of administration of alfentanil. The mean alfentanil requirement in patients with Crohn's disease was significantly greater than in control patients ($P < 0.01$). There was no correlation between MAI and alfentanil requirements in the patients with Crohn's disease. Plasma concentrations of AAG in the samples collected 15 min after induction in patients with Crohn's disease were significantly greater than those in the control group ($P < 0.02$). Plasma concentrations of AAG in patients with Crohn's disease were smaller ($P < 0.001$) at the time of extubation than 15 min after the induction of anaesthesia. There was a moderate correlation between plasma concentration of AAG and MAI in patients with Crohn's disease: AAG concentrations increased with increasing MAI, both after induction ($r = 0.73$) and at the time of extubation ($r = 0.70$).

Protein binding could be determined in eight control patients and in all the patients with Crohn's disease. There was no significant difference in protein binding between the groups, either before or after the operation. However, the free fractions of alfentanil at extubation were greater than those after induction in the group with Crohn's disease ($P < 0.02$).

Inadequate blood sampling precluded formal pharmacokinetic analysis in one control patient.

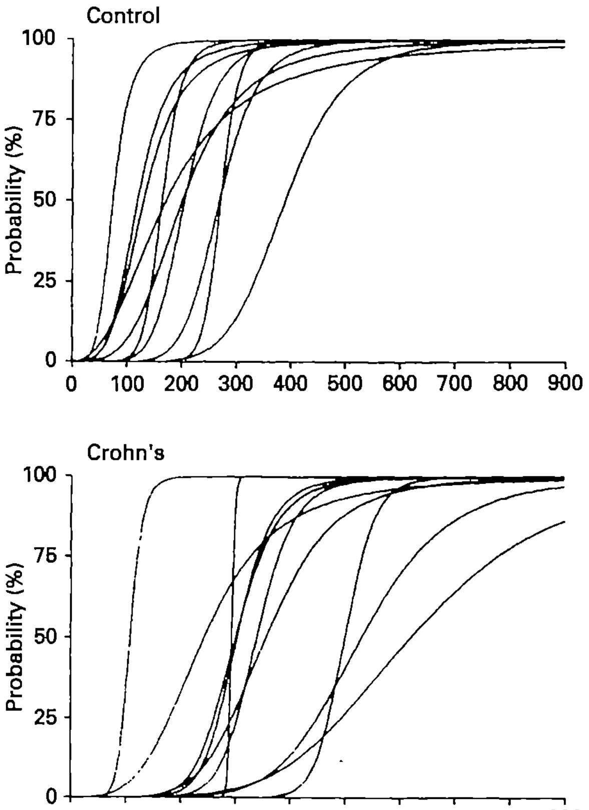

FIG. 1. Alfentanil plasma concentration–effect (probability of no response) curves for each individual patient during abdominal surgery in control patients (upper panel) and in patients with Crohn's disease (lower panel). Patients were also receiving 66% nitrous oxide in oxygen. The curves were obtained from the quantal responses of the individual patient to surgical stimulation using non-linear regression. $C_{P,50}$ values are presented in tables V and VI.

Pharmacokinetic data were similar in both groups (tables V, VI), including total plasma clearance (*Cl*) and volume of distribution (V^{ss}) normalized for body weight as presented, but also for data not corrected for body weight (mean total plasma

TABLE V. *Control patients; pharmacokinetic and pharmacodynamic parameters. † Concentration in patient that required naloxone ignored in statistical analysis.* $T_{\frac{1}{2}}$ = *Terminal half-life;* Cl = *total body clearance;* V^{ss} = *steady state volume of distribution;* C_P^{ext} = *plasma alfentanil concentration at extubation;* $C_{P,50}$ = *plasma alfentanil concentration for which the probability of no response during abdominal surgery is 50%. * Compared with patients with Crohn's disease (table VI); ns = not significant*

Patient No.	$T_{\frac{1}{2}}$ (min)	*Cl* (ml kg^{-1} min^{-1})	V^{ss} (litre kg^{-1})	C_P^{ext} (ng ml^{-1})	$C_{P,50}$ (SE) (ng ml^{-1})
1	—	—	—	96	130 (27)
2	68	9.6	1.20	210	201 (29)
3	82	4.7	0.58	109	119 (20)
4	43	6.2	0.39	133	271 (15)
5	103	7.6	0.72	71	171 (63)
6	56	5.2	0.73	153	164 (11)
7	88	4.3	0.55	(222)†	389 (32)
8	76	3.4	0.31	151	205 (19)
9	132	2.5	0.43	196	269 (23)
10	82	14.0	1.20	43	74 (8)
Mean	81	6.4	0.68	129	199
SD	26	3.6	0.33	55	91
P*	ns	ns	ns	< 0.05	< 0.02

TABLE VI. *Patients with Crohn's disease: pharmacokinetic and pharmacodynamic parameters. † Concentrations in patients that required naloxone ignored in the statistical analysis. ‡ Midrange between greatest concentration with response and smallest concentration without response; because of a lack of overlap in the concentrations with and without a response, curve fitting was impossible in this patient.* $T_{\frac{1}{2}}$ = *Terminal half-life;* Cl = *total body clearance;* V^{ss} = *steady state volume of distribution;* C_P^{ext} = *plasma alfentanil concentration at extubation;* $C_{P,50}$ = *plasma alfentanil concentration for which the probability of no response during abdominal surgery is 50%. * Compared with control patients (table V); ns = not significant*

Patient No.	$T_{\frac{1}{2}}$ (min)	*Cl* (ml min^{-1} kg^{-1})	V^{ss} (litre kg^{-1})	C_P^{ext} (ng ml^{-1})	$C_{P,50}$ (SE) (ng ml^{-1})
1	61	6.6	0.47	101	108 (7)
2	74	6.1	0.65	247	303 (18)
3	144	2.7	0.59	797	—
4	76	7.5	0.84	107	—
5	43	6.5	0.73	219	243 (40)
6	86	6.0	0.77	287	339 (18)
7	75	6.2	0.84	381	530 (46)
8	62	8.4	0.91	208	355 (35)
9	137	3.5	0.66	224	293‡
10	59	3.4	0.41	(338)†	500 (15)
11	76	3.4	0.52	468	619 (66)
12	70	8.4	0.97	(214)†	300 (21)
Mean	80	5.7	0.70	304	359
SD	30	2.0	0.18	207	151
P*	ns	ns	ns	< 0.05	< 0.02

clearance not corrected 431 (191) ml min^{-1} in the control group and 342 (119) ml min^{-1} in the Crohn group; mean uncorrected V^{ss} 47 (19) litre in the control group and 42 (12) litre in the Crohn group).

The plasma concentration *vs* probability of no response curves for the intra-abdominal period of surgery of individual patients are shown in figure 1. The plasma alfentanil concentrations for which the probability of no response during surgery was 50% ($C_{P,50}$) could be determined in 20 of the 22 patients (tables V, VI). Values were significantly greater in patients with Crohn's disease than in control patients ($P < 0.02$). Within the group of patients with Crohn's disease there was a moderate correlation between MAI and $C_{P,50}$ ($r = 0.73$), but this was based mainly on the two most extreme observations.

Nineteen patients regained spontaneous ventilation within 10 min of discontinuation of nitrous oxide at the end of the operation. Naloxone was administered before tracheal extubation to two patients with Crohn's disease (0.04 mg and 0.08 mg) and to one patient in the control group (0.08 mg). Plasma concentrations of alfentanil at the time of extubation (C_P^{ext}) in patients who did not need naloxone were greater in patients with Crohn's disease than in the control group ($P < 0.05$).

When questioned on the day after surgery, no patient had any recall of the anaesthesia or surgical period. More than 50% of the patients had no recall of insertion of the venous and arterial cannulae.

DISCUSSION

The pharmacokinetics of alfentanil in adult surgical patients have been investigated extensively [10–15]. In these studies, mean values for $T_{\frac{1}{2}}$, *Cl* and V^{ss} were in the ranges 1.2–2.0 h, 3–8 ml kg^{-1} min^{-1} and 0.3–0.8 litre kg^{-1}, respectively. In the present study, we found similar values for these pharmacokinetic parameters in both patient groups; the study did not reveal differences in the pharmacokinetics of alfentanil in patients with Crohn's disease compared with control patients. Given the relatively small numbers of patients and the observed interindividual variations, it cannot be excluded that differences between the study groups have been missed, and therefore definite conclusions cannot be drawn in this respect. However, if any differences exist, they are likely to be small, as would be their contribution to the observed significant difference in the dose requirements of the two groups of patients.

A basic premise in examining the pharmacodynamics of alfentanil is that the measured plasma concentrations are close to equilibrium with the concentrations at the site of action. Support for this premise comes from studies examining plasma concentration–EEG effect relationships [12,13]. These studies have demonstrated a close correlation between the increase and decline of the plasma alfentanil concentrations with the onset and recovery of EEG changes, indicative of opioid effect. Estimated effect–plasma concentration equilibration half-times were approximately 1 min.

In previous studies on the concentration–effect relationship of alfentanil, variable values of $C_{P,50}$ have been reported, depending on the type of surgery and alcohol intake of the patients studied [16,17]. In order to create a matched control group, we selected our patients carefully, trying to avoid all factors known to influence alfentanil pharmacodynamics. All the patients studied underwent major abdominal surgery. The type of operation was comparable between patients with Crohn's disease and control patients and all operations were performed by the same surgeon. Furthermore, the presence or absence of responses was always judged by the same staff anaesthetist and trainee. Ideally, at least one of the observers should have been blinded to the diagnosis of the patients undergoing surgery, but this was not possible as, in our hospital, it is standard practice that a gastroenterologist is present during the course of the operation in order to discuss the findings and subsequent surgical management of the patient with the surgeon. We feel confident that our knowledge of diagnosis did not influence administration of alfentanil, as adjustments of the maintenance infusion rates were regulated by a set of precisely defined, predetermined conditions and because most of the responses in both the control (54 of 68) and Crohn's disease patients (90 of 102) involved haemodynamic changes that were measured objectively. This view is supported also by the fact that there was no difference between the two patient groups in naloxone requirement after operation.

The mean alfentanil $C_{P,50}$ was significantly ($P < 0.02$) greater in patients with Crohn's disease (359 ng ml^{-1}) compared with the control group (199 ng ml^{-1}). The mean value for $C_{P,50}$ in our control group was less than values reported by Lemmens and colleagues [8,18] and Ausems and colleagues [16] for patients undergoing similar operations. Differences between anaesthetic regimens may be responsible for these disparate observations. Premedication in our study was midazolam, which might be more potent than temazepam, as used in the studies of Lemmens and colleagues [8, 18] and Ausems and colleagues [16]. The fact that the loading dose of alfentanil was supplemented with thiopentone to ensure a smooth induction in our patients may have decreased the alfentanil requirement.

One factor which might influence drug pharmacodynamics is concurrent medication. In this respect, the two patient groups were not comparable. All but one patient in the group with Crohn's disease were receiving corticosteroids, another anti-inflammatory drug, or both, for treatment of their bowel disease. In the control group, only one patient took medication, consisting of metoclopramide and an antacid preparation.

Glucocorticosteroids are known to contribute to pain relief in some situations and are often administered as co-analgesics in the treatment of cancer pain [19–21]. They are effective also in reducing postoperative pain after oral surgery and lumbar discectomy [22–24]. Although the analgesic effect of corticosteroids has been attributed to their ability to reduce inflammatory swelling, no correlation was found between the reduction in swelling and pain when corticosteroids were administered to patients after oral surgery [23,25]. This suggests that corticosteroids may have specific analgesic properties. One would expect, therefore, that patients receiving corticosteroids perioperatively would require less opioid for postoperative pain relief. However, we found that patients with Crohn's disease receiving glucocorticosteroids required more opioid than patients in the control group.

Many of the patients with Crohn's disease received, in addition, sulphasalazine type drugs before operation. We are not aware of any studies documenting the influence of these drugs on the pharmacodynamics of opioids. To our knowledge, sulphasalazine does not affect pain perception in the way corticosteroids are known to do.

A factor that must be considered when comparing plasma concentration–effect relationships is protein binding. In general, total plasma concentrations are used for determining plasma concentration–effect relationships, although drug effect is believed to be related more closely to free drug concentrations. A change in the plasma concentration–effect relationship of a drug may sometimes be explained by altered protein binding. Alfentanil, in common with many other basic drugs, binds avidly to AAG, a plasma protein known as one of the acute phase proteins [2,26]. An increase in the plasma concentration of AAG may be expected to result in an increased binding of alfentanil to this protein and, therefore, in a decreased free fraction of alfentanil. This has been described for other basic drugs in various disease states associated with increased plasma concentrations of AAG [27,28].

Crohn's disease is associated with increased plasma AAG concentrations [3,5]. Initial plasma concentrations of AAG were increased in the patients with Crohn's disease in this study, and showed a moderate correlation with the severity of the disease as reflected in the MAI. However, the increased AAG concentrations were not associated with an altered degree of protein binding of alfentanil; free alfentanil fractions did not differ from those in control patients. This unexpected observation has also been reported by Belpaire and Bogaert [4] in patients with rheumatoid arthritis which, in common with Crohn's disease, is also an inflammatory disorder associated with increased plasma concentrations of AAG. These authors studied alfentanil binding in the serum of patients with various clinical conditions associated with increased plasma AAG concentrations such as renal failure, myocardial infarction and rheumatoid arthritis. None of the patients had Crohn's disease. They found significant increases in plasma concentrations of AAG and alfentanil binding in patients with myocardial infarction, whereas in patients with rheumatoid arthritis, binding of alfentanil was unchanged in spite of even greater increases in plasma concentrations of AAG. The percentages of free alfentanil in these patients were similar to those found in their control patients. Belpaire and Bogaert suggested that endogenous compounds or other drugs may possibly be responsible for the observed inhibition of alfentanil binding in patients with rheumatoid arthritis. In patients with Crohn's disease the same hypothesis may apply.

Theoretically, increased protein binding may delay the initial drug distribution to the tissues because initial free (diffusible) drug concentrations are smaller. This would be expected to increase the dose requirements. However, this is likely to be important only when drug input is fast, such as after a bolus injection or with short infusions. When drug input is slow, such as with prolonged infusions, any change in protein binding of alfentanil is likely to be buffered by its more extensive tissue binding, so that protein binding—by influencing tissue distribution—should have little effect on free alfentanil concentrations. Also, as alfentanil is removed from the body by metabolism in the liver and because its hepatic extraction ratio is relatively small (< 0.3), increased protein binding (decreased free fraction) would be expected to decrease the clearance of alfentanil. Consequently, if pharmacodynamics are unaltered, an increase in protein binding should not necessarily enhance dose requirements for alfentanil.

In conclusion, we have demonstrated that Crohn's disease has little or no effect on the pharmacokinetics of alfentanil. However, plasma concentrations of alfentanil required to achieve a given clinical effect were greater in patients with Crohn's disease compared with control patients. This increase in required plasma concentration was not a result of altered plasma protein binding, in spite of the markedly increased plasma concentration of AAG. The increased dose requirement of alfentanil in patients with Crohn's disease may be related to a change in the pharmacodynamics of alfentanil in these patients. We do not know if the altered pharmacodynamics is a direct effect of the disease, or an indirect effect of concomitant medication.

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ELECTROACUPUNCTURE IN ANAESTHESIA FOR HYSTERECTOMY

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SUMMARY

We have studied the effects of electroacupuncture at classical acupuncture points, applied before and during surgery in patients undergoing hysterectomy, on postoperative pain and metabolic stress responses in a prospective, randomized and patient-blinded manner. Fifty otherwise healthy women were allocated randomly to receive or not receive electroacupuncture. Electroacupuncture was begun 20 min before skin incision and continued to the end of surgery. All patients received similar general anaesthesia and all received patient-controlled analgesia (PCA) after operation. Postoperative pain in the two groups was evaluated by recording analgesic requirements by PCA and by pain-rating performed by patients and nursing staff. There were no significant differences between the two groups in postoperative analgesic requirements, pain-rating or metabolic stress responses. (Br. J. Anaesth. 1993; **71**: 835–838)

KEY WORDS

Acupuncture. Pain: postoperative, patient-controlled analgesia. Surgery: hormonal response.

Postoperative peripheral electrostimulation has been suggested to have a beneficial effect on postoperative pain when given as either transcutaneous nerve stimulation or electroacupuncture [1–3]. It has also been suggested that peripheral electrostimulation may produce analgesia during operation [4–6]. One of these studies suggested that peripheral electrostimulation given before and during the painful stimulus may produce prolonged analgesia [4]. In a previous randomized study using electroacupuncture after operation, we found a significant reduction in pethidine requirements after operation in the group given electroacupuncture [1]. In recent years there has been interest in various anaesthetic techniques which may modify the stress response to surgery [7–13], but only a few have examined electroacupuncture [11].

In this study, we have examined the effect of pre- and peroperative electroacupuncture on postoperative pain and the metabolic stress response to anaesthesia and surgery.

PATIENTS AND METHODS

This prospective, randomized and patient-blinded study of electroacupuncture was performed before and during operation in women undergoing elective hysterectomy. The study was blinded to the nursing staff performing postoperative pain rating, but not to the anaesthetist performing anaesthesia. The study was approved by the Local Human Investigations Committee and informed consent was obtained.

We studied 50 otherwise healthy women of mean age 45 yr (range 33–66 yr). On the day before operation, weight, arterial pressure, heart rate and handgrip strength (a marker of fatigue) were recorded and the patient-controlled analgesia system (PCAS) demonstrated. The patients were asked if they had previously experienced transcutaneous nerve stimulation, electroacupuncture or classical acupuncture. Preoperative anxiety was assessed by the patient on a scale from 1 to 4 (no anxiety, slight, moderate and very anxious). The acupuncture loci were identified in all patients the day before surgery. All patients were premedicated with oral diazepam 0.2 mg kg^{-1} 2 h before anaesthesia. Arterial pressure, ECG and Sp_{O_2} were monitored and 0.9% sodium chloride was given i.v. Pethidine 1.5 mg kg^{-1} i.v. was given and anaesthesia induced with propofol 1.2–1.5 mg kg^{-1} i.v. Tracheal intubation was facilitated by administration of vecuronium 0.1 mg kg^{-1}. Ventilation was controlled manually and anaesthesia maintained with 66% nitrous oxide in oxygen, continous infusion of propofol 4–8 mg kg^{-1} h^{-1}; pethidine 0.5 mg kg^{-1} was given before skin incision and thereafter as required, at the discretion of the anaesthetist. A Pfannenstiel incision was used in all operations.

Electroacupuncture

Immediately after induction of anaesthesia, the patients were allocated randomly to receive either electroacupuncture (group EA+) or no electroacupuncture (group EA−) (25 in each group). The

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loci for electroacupuncture were selected from standardized acupuncture formulae for anaesthesia for hysterectomy [1]: GV2 = Govenor vessel 2, Jao-Iu, in the dorsal midline between the coccyx and sacrum; GV4 = Govenor vessel 4, Ming-men, in the dorsal midline below the spinal process of the 2nd lumbar vertebra; B 32 = bladder 32, Ciliao, bilaterally in the second sacral foramen; SP 6 = spleen 6, Sanjiniao bilaterally on the medial edge of the tibia, four fingerwidths above the tip of the internal malleolus; ST 36 = stomach 36, Zusanli, one fingerwidth lateral to the tuberositas tibia.

After induction, the patients in group EA+ were placed on the side. Sterile transparent dressings were placed over each locus. Acupuncture needles were sterilized solid stainless steel, 10 cm long and 30-gauge. They were inserted to the prescribed depth for each locus, bent back against the plastic and taped in place, with wires connected to a constant current source. The patient was turned supine again. Electroacupuncture was commenced using a constant current source with pulse width 320 ms, approximately 12 V, and chain frequencies 10 Hz and 100 Hz [1], for 20 min before skin incision was allowed. A similar period passed before incision in group EA−. Electroacupuncture was given throughout the operation to group EA+; it was discontinued and the needles removed at the end of surgery, while the patient was still anaesthetized.

Patient-controlled analgesia and pain rating

After tracheal extubation and transport to the recovery room, all patients in both groups were connected to a patient-controlled analgesia system (PCAS) providing pethidine i.v. with boluses of 20 mg in the first 1 h and 10 mg in the subsequent 3 h with a lockout time of 10 min. Doses were registered on a chart recorder. Arterial pressure, heart rate and Sp_{O_2} were recorded every 30 min for the first 2 h and thereafter at 1-h intervals. Supplementary oxygen 2 litre min^{-1} was given via a nasal catheter. All patients were given prophylactic metoclopramide 12.5 mg i.v. as antiemetic. No additional analgesia was administered by the nurse in the recovery room.

One hour after arrival in the recovery room, the patient was asked to complete a 100-mm vertical visual analogue scale (VAS score) for pain at rest and after coughing and to perform a pain rating on a scale 1–4 (none, slight, moderate and heavy pain). A contemporary rating on the same scale was performed by a recovery nurse. These recordings were repeated after 4 h, the PCAS disconnected and the patient discharged to the ward.

Stress markers

Venous blood samples were obtained and the temperature recorded on the morning of admission and on the first and second days after operation. Blood concentrations of glucose, transferrin and orosomucoid, white and red blood cell counts and serum concentrations of haemoglobin, TSH and T4 were measured. Venous samples were obtained 1, 2 and 6 h after skin incision for measurement of T4, TSH, and glucose. Urine was collected for 24-h periods (08:00 to 08:00) on the day before operation, the day of operation and the first and second days after operation for measurement of daily urinary cortisol excretion. Handgrip strength (dominant hand with patient in supine position) was recorded on the morning before and the first and second days after surgery.

Statistics

The size of the groups was calculated using power analysis with a type 1 error of 0.05, a type 2 error of 0.20 and a minimal clinical difference of interest between groups of pethidine 20 mg used in the recovery room. Statistical analyses were performed using non-parametric tests: Wilcoxon rank sum test for paired differences and the Multiple ANOVA for analyses of variance.

RESULTS

The two groups were similar in age and weight (table I). Two patients in each group had experienced acupuncture before. There was no difference in distribution of anxious patients between groups, the majority being slightly anxious. There were no problems in placing the needles, the operations were

TABLE I. *Patient data (mean (range)).* † *Between groups*

	Age (yr)	Weight (kg)	Duration of anaesthesia (min)	Propofol requirement (mg)
Group EA+	45	68	133	690
(*n* = 25)	(33–58)	(53–96)	(95–180)	(180–900)
Group EA−	43	64	120	605
(*n* = 25)	(33–60)	(54–92)	(85–180)	(380–850)
†*P*	0.62	0.47	0.07	0.12

TABLE II. *Mean (range) pethidine requirements during operation, during 1 h and 2 h after operation and the total postoperative requirement for pethidine in the recovery room.* † *Between groups*

	Pethidine requirement (mg)			
	During operation	0–60 min	0–120 min	0–240 min
Group EA+	147	57	82	139
(*n* = 25)	(100–250)	(0–100)	(0–180)	(20–230)
Group EA−	142	66	90	150
(*n* = 25)	(100–220)	(20–120)	(20–180)	(50–250)
†*P*	0.19	0.33	0.54	0.48

TABLE III. *Mean (range) of visual analogue scale (VAS) scores for pain, at rest and while coughing. No statistical differences between groups*

	VAS score for pain			
	At rest		Coughing	
	2 h	4 h	2 h	4 h
Group EA+	51	43	64	58
(*n* = 25)	(12–95)	(5–80)	(22–95)	(17–95)
Group EA−	51	65	63	87
(*n* = 25)	(20–90)	(20–90)	(30–90)	(32–90)

TABLE IV. *Mean (range) of blood samples and 24-h urinary cortisol measurements in patients receiving electroacupuncture (group EA+) or no treatment (group EA−). Normal values are indicated. No statistical differences between groups*

	Before op.		Day 1		Day 2		Day 3	
Normal range	EA+ ($n = 25$)	EA− ($n = 25$)	EA+ ($n = 25$)	EA− ($n = 25$)	EA+ ($n = 25$)	EA− ($n = 25$)	EA+ ($n = 25$)	EA− ($n = 25$)
Urinary cortisol	135	107	1659	1324	308	253	170	287
(nmol litre^{-1}) 50–230	(39–279)	(38–195)	(148–4405)	(102–3694)	(55–1029)	(53–1169)	(64–289)	(57–2025)
Transferrin	42	40			33	32	30	30
(μmol litre^{-1}) 22–55	(30–64)	(32–54)			(20–58)	(24–43)	(21–44)	(21–44)
Orosomucoid	0.8	0.7			0.86	0.89	1.22	1.23
(g litre^{-1}) 0.4–1.2	(0.37–1.3)	(0.5–0.93)			(0.57–1.24)	(0.6–1.64)	(0.1–1.1)	(0.81–1.69)
Leucocytes	5.8	6.7			9.8	9.7	9.1	8.6
($\times 10^9$ litre^{-1}) 4.0–10.0	(3.6–9.5)	(3.3–13.2)			(6.9–15.2)	(6.2–15.2)	(6–12.8)	(4.5–14.3)
T4	99	99			85	86	95	95
(nmol litre^{-1}) 60–140	(83–104)	(69–144)			(63–134)	(55–124)	(69–135)	(71–135)
TSH	1.8	1.4			1.8	1.4	1.7	1.5
(mu. litre^{-1}) 0.4–4.0	(0.4–7.5)	(0.6–4.4)			(0.3–4.7)	(0.3–6.8)	(0.4–5.4)	(0.6–5.0)
Blood sugar	4.8	4.8			4.9	4.7	4.7	4.9
(mmol litre^{-1})	(2.7–7.5)	(3.7–5.8)			(4.0–7.8)	(3.3–6.1)	(2.9–6.0)	(3.8–7.1)
Temperature	36.6	36.6			37.3	37.2	37.6	37.7
(°C)	(35.8–37.6)	(36.0–37.5)			(36.7–38.1)	(36.4–37.6)	(37.3–38.4)	(37.4–38.2)
Handgrip strength	0.8	0.8			0.8	0.7	0.9	0.7
(Barr)	(0.7–1.2)	(0.6–1.3)			(0.5–1.1)	(0.4–0.8)	(0.5–1.4)	(0.5–1.1)

TABLE V. *Mean (range) blood sugar and serum TSH concentrations just before incision and 1 and 6 h after incision in patients receiving electroacupuncture (EA+) or no treatment (EA−). Significant difference from before incision within group:* *$P < 0.05$*. No significant difference between groups*

	Blood sugar (mmol litre^{-1})			TSH (mu. litre^{-1})		
	Before incision	1 h after incision	6 h after incision	Before incision	1 h after incision	6 h after incision
Group EA+	5.2	5.6	7.5	4.2	4.03*	1.7*
($n = 25$)	(3.5–6.7)	(0.28–7.4)	(4.1–7.8)	(0.81–19.1)	(0.74–12.81)	(0.31–6.97)
Group EA−	5.3	5.6	6.5	2.9	2.7*	1.2*
($n = 25$)	(3.6–7.7)	(3–7.1)	(4.6–10.1)	(0.82–9.12)	(0.71–7.91)	(0.39–3.41)

uneventful and no patient required blood transfusion. There was no significant difference in duration of anaesthesia between the two groups.

There was no significant difference in pethidine consumption between groups for cumulative periods of 60, 120 and 240 min after operation (table II) or for VAS scores (table III).

There was no significant difference between the two groups in the markers of metabolic stress response and no significant difference in handgrip strength throughout the study, or significant change within both groups from preoperative to postoperative values (tables IV and V).

DISCUSSION

This study was prospective, randomized and patient-blinded, but observer blinded only for the postoperative period as blinding the anaesthetist would have been difficult. Reproducibility was attempted by precise specification of acupuncture loci and mode of stimulus and assessment of effects by the use of both subjective and objective measures—mainly VAS score and PCAS.

In a previous randomized and patient-blinded study [1], electroacupuncture was used after operation in women undergoing elective hysterectomy, while they were still anaesthetized. Postoperative analgesia was assessed using PCAS consumption of pethidine. There was 40% less pethidine used by the group given electroacupuncture. The failure of the present study to demonstrate an effect of electroacupuncture may be attributed to several reasons.

It is possible that the effects of electroacupuncture given before and during operation may have terminated before the postoperative observation period. This accords with the results of our previous study, in which the effects of postoperative electroacupuncture were significant only within the first 2 h after operation. Although we may have expected to observe an effect on the peroperative requirement for pethidine in the EA+ group, such an effect may have been masked by the relatively large amounts of pethidine used for induction and maintenance (1.5 mg kg^{-1} at induction and 0.5 mg kg^{-1} at skin incision), which may also have induced a pre-emptive effect [14]. In addition, in the present study we used propofol rather than thiopentone as in our previous study, and this may have been a confounding factor.

The surgical stress response was not modified by pre- and peroperative electroacupuncture as was also the case in two other studies of electroacupuncture [11, 13]. Kho and colleagues used electroacupuncture supplemented with pethidine in awake patients, but the study was performed without a control group [11]. In a later study [13], the same group used electroacupuncture after induction of general anaesthesia but 30 min before surgery; there was no difference between the EA+ and EA− groups.

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EFFECTS OF SMALL CONCENTRATIONS OF ISOFLURANE ON SOME PSYCHOMETRIC MEASUREMENTS

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SUMMARY

We have investigated the effects of 9.5% and 14.1% MAC concentrations of isoflurane on some psychometric measurements. Both concentrations depressed peak saccadic velocity ($P < 0.01$), choice reaction time ($P < 0.05$) and visual analogue scores for sedation ($P < 0.05$), but not the critical flicker fusion threshold. The incidence of errors in saccade tasks increased in a dose-related fashion, which made analysis of peak saccadic velocity less accurate at more than 10% MAC. The percentage error itself was an indicator of the depth of sedation. All the objective measures correlated highly with the estimated brain tension of isoflurane ($r^2 = 0.86$–0.96), but not the visual analogue score for sedation ($r^2 = 0.51$). This suggests that a combination of peak saccadic velocity, percentage error and choice reaction time is a potentially useful batch of tests to measure recovery from anaesthesia. (Br. J. Anaesth. 1993; **71**: 839–844)

KEY WORDS

Anaesthetics volatile: isoflurane. Brain: monitoring, saccadic eye movements, choice reaction time, critical flicker fusion threshold.

The pressure to develop day-stay surgery ensures continuing interest in assessment of recovery from anaesthesia. There has been no shortage of publications on techniques for doing this. It has been shown that, in a research setting, the peak velocity of saccadic eye movements (PSV) is a sensitive indicator of central nervous system depression [1,2], able to detect the effects of 5% and 10% MAC concentrations of several inhalation anaesthetics and clinically comparable infusion rates [3] of propofol, in a dose-related way [4–6]. Other techniques, such as choice reaction time (CRT), critical flicker fusion threshold (CFFT) and subjective assessment of sedation have also been used widely [7], but generally at somewhat deeper levels of sedation.

There is some evidence [8] that the ability of the subject to perform a saccadic task is impaired at levels of sedation deeper than those used so far in studying inhalation agents. It is also unclear if the other measures referred to above are as sensitive as PSV. Accordingly, we have investigated this by comparing PSV, CRT, CFFT and subjective sedation by visual analogue scoring (VAS) at 10% and 15% MAC end-tidal steady-state concentrations of isoflurane to determine if there were any differences between the tests and if any effects were dose-related.

SUBJECTS AND METHODS

We studied six drug-free, healthy volunteers. They were aged 21–33 yr, two males and four females. The study was approved by the District Ethics Committee and informed consent was obtained. Each volunteer had three treatment sessions at the same time of the day at intervals of 1 week or more. Each session consisted of assessment while breathing either air (A), 10% (I_{10}) or 15% (I_{15}) MAC concentrations of isoflurane. Isoflurane 1.28% was assumed to equal 1 MAC for this age group [9]. The agents were administered in a random order determined by opening the next envelope in a pre-generated set of six sets of the three sequences. The study was performed in a sound-attenuated laboratory and at constant ambient illumination. Each volunteer was allowed to practise the saccadic eye movement, CRT and CFFT tasks at least 10, 50 and 12 times, respectively, until there were no further learning effects.

Breathing system

Concentrations of 0.2–0.3% isoflurane in air were delivered using the breathing system described previously [4]. Briefly, air from a flowmeter was passed through a calibrated Fortec vaporizer and the output concentration diluted with air via a second calibrated flowmeter to a total fresh gas flow of 15–21 litre min^{-1}. The inspired concentrations were adjusted to maintain as near 10% and 15% MAC of end-tidal concentrations as possible (0.128% and 0.192%). Each volunteer wore a Royal Air Force pilot's face mask with non-rebreathing valves, adjusted to avoid leaks. Two fine-bore sample tubes were attached to the mask. Isoflurane concentrations were monitored continuously with a Datex Normac infra-red analyser through one of the sample tubes to identify the alveolar plateau. Isoflurane standards in

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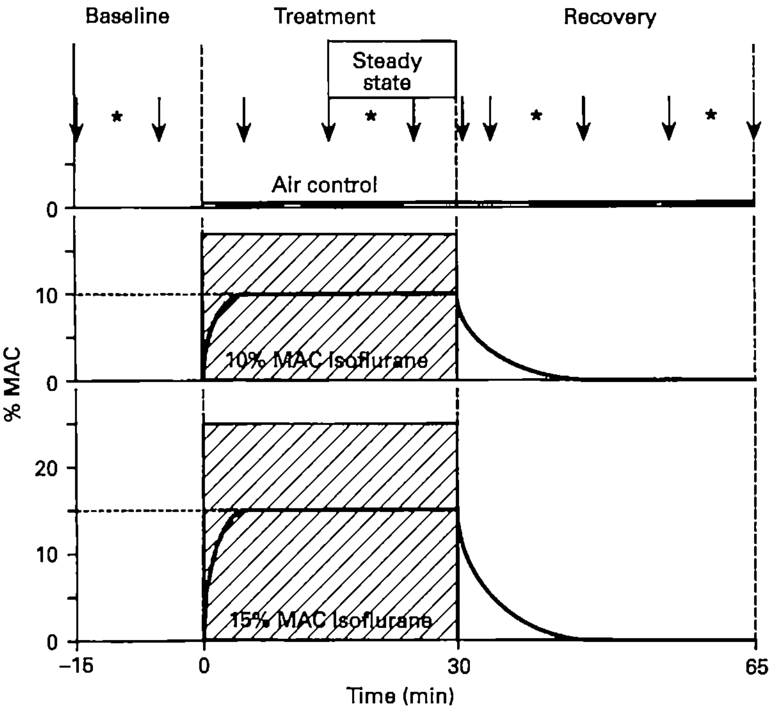

FIG. 1. The study sequence in air, 10% MAC and 15% MAC isoflurane sessions. ↓ = PSV measurement; *measurement of CRT and CFFT; ▨ = inspired concentration; — = alveolar concentration.

the range 0.05–0.2 vol% were prepared as described previously [4]. These standards were used to calibrate the Datex Normac using the halothane position: the Normac was attached to a two-channel chart recorder and the concentrations recorded continuously by amplifying the output so that 0.1% equalled 10 mm on the recorder (target concentrations were 0.128% and 0.192% = 12.8 mm and 19.2 mm, respectively).

Alveolar gas samples were drawn through a three-way tap attached to the other fine-bore tube before and after each set of PSV measurements. To obtain the samples, the subject exhaled to residual volume and the sample was drawn during the alveolar concentration plateau. On the chart recorder, the baseline fluctuated because of exhaled water vapour and it was thus thought prudent to measure the isoflurane concentrations by gas–liquid chromatography using the standard gas mixtures for calibration. The alveolar concentrations of isoflurane measured by the Normac were in good agreement with the concentrations measured by gas–liquid chromatography.

Saccadic eye movement measurements

Details of the eye movement recording system have been reported previously [4–6]. In brief, saccades were generated by having the subject follow the horizontal movements of an illuminated target at symmetrical eye displacements of 10, 20, 30 and 40°. Sixty such target movements were presented to the subject on each occasion. Eye position was monitored from the electro-oculogram. An IBM-compatible (Opus PC II) microcomputer controlled the target movements, digitized the data and stored them on disc. Saccades were analysed according to the method of Marshall and Richens [10] and the interpolated PSV value at 35° was taken as the measure. Aberrant eye movements were excluded from analysis according to the criteria of Griffiths, Marshall and Richens [1]. The percentage of aberrant eye movements was obtained by dividing the number of target movements which were excluded by the total number of target movements and expressed as a percentage. This we refer to as "error %".

Each session lasted 80 min. It started with a 15-min period breathing room air without the mask, followed by 30-min inhalation of air, 10% or 15% MAC of isoflurane and then by 15 min breathing air from the face mask. The last 20 min was a further recovery period breathing room air without the mask. PSV was measured at 10-min intervals and an additional measurement was taken 1 min after isoflurane was discontinued (fig. 1).

Choice reaction time

Six stimulus lights and corresponding buttons on the Leeds psychomotor tester [11] were presented to the subject. The lights were illuminated in random order. From the ready position (central button), the time taken for the subject to extinguish the light by touching the corresponding button using a finger on the dominant hand was recorded as choice reaction time. The median of 21 measurements was recorded.

Critical flicker fusion threshold

The subject watched four light-emitting diodes on the Leeds psychomotor tester [11] at a distance of 1 m. The frequency of flicker was increased from 12 Hz to 50 Hz over 1 min and then decreased in a similar fashion. The subject pressed a button when the change from flicker to fusion or the reverse was observed. The mean of three measurements for

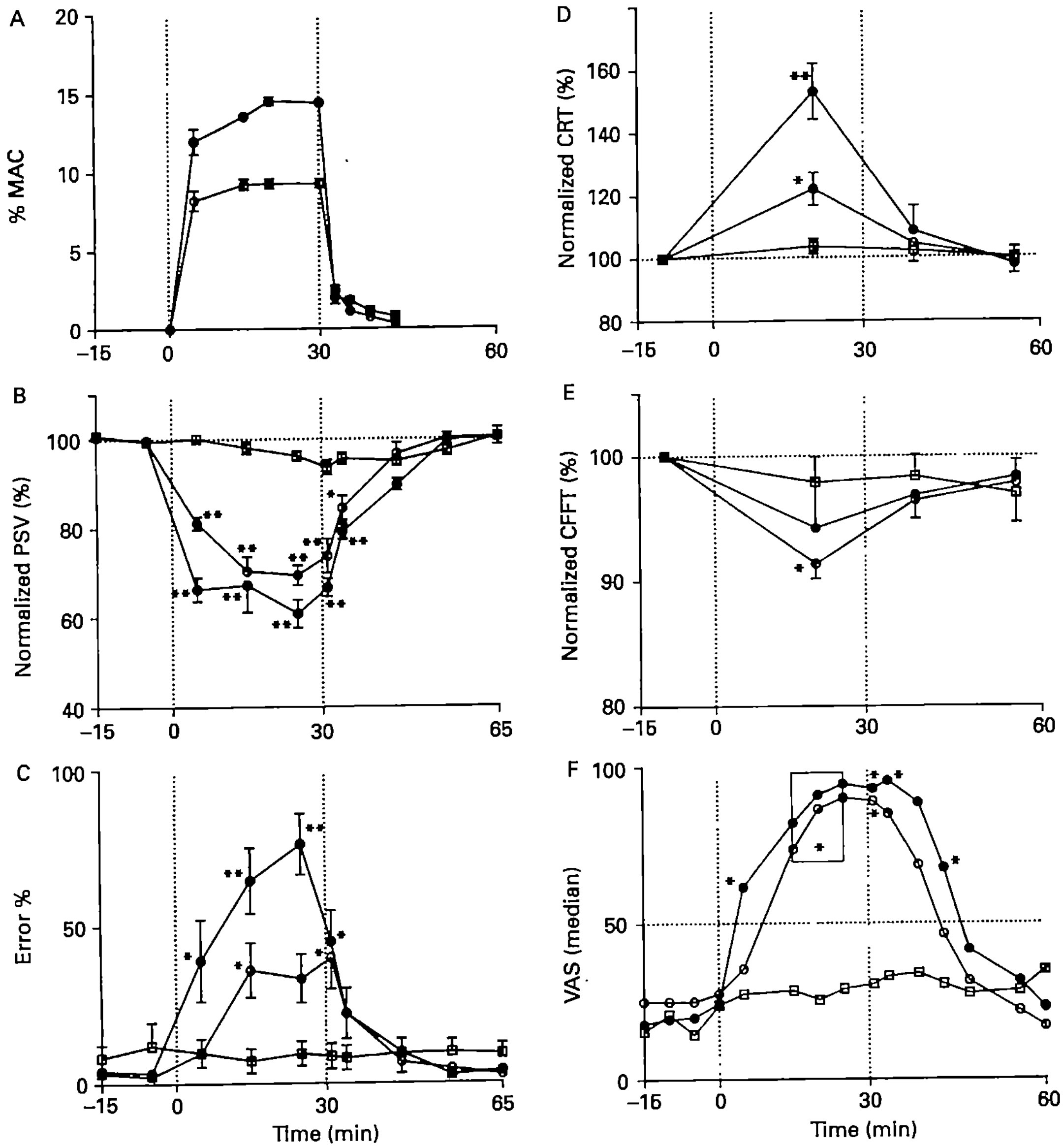

FIG. 2. Mean (SEM) effect of air (□), 10 % MAC (○) and 15 % MAC concentrations of isoflurane (●) in six volunteers. A: End-tidal concentrations as a percentage of MAC. B: Normalized peak saccadic velocity (%). C: Error % in saccadic task (%). D: Normalized choice reaction time (%). E: Normalized critical flicker fusion threshold (%). F: Visual analogue score for sedation where 0 = wide awake and 100 = very sleepy. (Box indicates the steady state values which were averaged for comparison.) $*P < 0.05$, $**P < 0.01$, compared with air.

downward and three upward shifts in frequency was taken.

CRT and CFFT were measured four times, once during each baseline and treatment period, 20 min after starting isoflurane and twice in the recovery period—10 and 20 min after isoflurane was discontinued (fig. 1).

Subjective assessment

Each subject was asked to assess their level of sedation by marking a 10-cm linear analogue scale just before each PSV and each set of CRT and CFFT measurements. The extremes were denoted as "wide awake" and "just before falling asleep". Subjects were also asked about their appreciation of odour, blurred vision, nausea and headache at the end of each treatment. At the completion of all three sessions, each subject was asked to rate the potency of the "agents" used in the three sessions.

Statistical analysis

PSV, error %, CRT and CFFT data were analysed by two-way ANOVA at each measurement time, with subject and treatment as main factors to obtain the residual variance. Significant differences at the $P < 0.05$ and $P < 0.01$ levels were identified by the Tukey multiple range test. The frequencies of detection of odour, blurred vision, nausea and headache were compared by Fisher's exact test.

RESULTS

Mean end-tidal concentrations of isoflurane were 9.5 (SEM 0.2)% and 14.1 (0.2)% of MAC at 15 and 25 min of the I_{10} and I_{15} sessions, respectively (fig. 2A). Both concentrations depressed PSV compared with air at all measurement points during administration ($P < 0.01$). At steady state (between

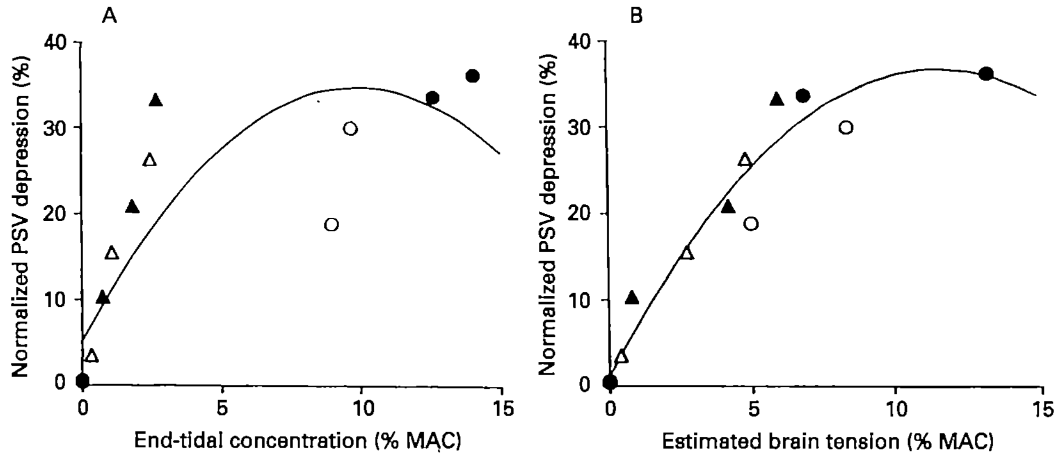

FIG. 3. A: Normalized PSV depression regressed on end-tidal concentration of isoflurane. B: Normalized PSV depression regressed on estimated brain tension of isoflurane. ○ = During inhalation of 10% MAC isoflurane; △ = recovery after discontinuing 10% MAC. ● = During inhalation of 15% MAC isoflurane; ▲ = recovery after discontinuing 15% MAC.

10 and 15 min) there were no significant differences between the effects produced by the 10% and 15% concentrations. PSV returned to pre-treatment values within 15 and 25 min of discontinuing 10% and 15% MAC concentration of isoflurane, respectively (fig. 2B). Error %, which measures the effect of isoflurane in reducing the ability of the subject to perform the saccade task, increased significantly in a dose-related fashion (fig. 2C). Error % returned to pre-treatment values within 5 min of discontinuation of both concentrations.

Isoflurane increased CRT in a dose-related fashion (fig. 2D), the 10% and 15% concentrations producing a 22% ($P < 0.05$) and 53% ($P < 0.01$) increase, respectively, which returned to control values within 10 min of discontinuing treatment. CFFT was depressed by both concentrations but, because of the variability, only the 10% MAC concentration of isoflurane caused a significant ($P < 0.05$) but small (−8.7%) change (fig. 2E). Significant changes, in the direction of "Sleepy", were produced in the median VAS scores by both concentrations at steady state (fig. 2F).

Values of r^2 were obtained from regressing each measure on both the end-tidal concentrations and the estimated brain tensions, the latter estimated from the equation:

$$\text{estimated brain tension} = \text{end-tidal concentration} \times \frac{\text{brain tension}}{\text{alveolar tension}}$$

The brain : alveolar tension ratio was obtained from a computer simulation program, Uptake [Lack A, Shelly M, personal communication] as follows; the inspired concentration of 0.2% or 0.3% isoflurane, which was the average concentration used in I_{10} and I_{15} sessions, respectively, was simulated as though given for 30 min. The brain tension : alveolar tension was obtained from the simulation at each measurement point.

Simple regression lines were fitted to each measurement except for the normalized PSV depression, for which a quadratic regression line was fitted (fig. 3) as the quadratic term significantly improved the fit. Consistently greater r^2 values were obtained from regressing on the estimated brain tension than on the end-tidal concentration (table I). Very large values of r^2, around 0.9, were obtained from regressing all the objective measures on the estimated brain tension. In contrast, r^2 obtained from regressing VAS on the estimated brain tension was as little as 0.5.

TABLE I. *Subjective assessment of blurred vision, appreciation of odour, headache and feeling of nausea.* *P *< 0.01 compared with air*

	Air	10% MAC isoflurane	15% MAC isoflurane
Blurred vision			
Present	0	5	6*
Absent	6	1	0
Odour			
Present	0	6*	6*
Absent	6	0	0
Headache			
Present	1	1	1
Absent	5	5	5
Nausea			
Present	1	0	4
Absent	5	6	2

Subjective assessments of side effects are summarized in table I. All the subjects could detect the smell of isoflurane when it was used. All but one subject had blurred vision with both concentrations. The remaining subject had blurred vision only during the I_{15} session. Overall, all the subjects agreed that the air session was the least potent amongst the three. Only three subjects correctly identified 15% MAC as more potent than 10% MAC. The order in which the agents were given did not affect this identification.

DISCUSSION

The three objective measurements behaved differently. Of the three, PSV was the most sensitive at detecting sedation: both 10% and 15% MAC concentrations of isoflurane depressed PSV highly significantly. However, error % with 15% MAC was significantly greater than with 10% MAC, which made PSV analysis less accurate at 15% MAC than at 10% MAC, as fewer saccades were available for PSV analysis. Error % itself proved to be a good indicator of sedation, as it increased in a dose-related fashion.

Similarly, choice reaction time was affected by both concentrations of isoflurane. This agrees with previous studies that between 7% and 27% MAC concentrations of halothane, 9% and 24% MAC concentrations of enflurane [12] and about 20% MAC concentration of isoflurane significantly increase choice reaction time [13]. We found, however, that CRT was a more accurate measure of the depth of sedation than PSV at concentrations greater than 10% MAC because, first, CRT was affected in a dose-related fashion and second, the subjects were able to perform the CRT task without error at both concentrations.

We detected only a small effect of isoflurane on critical flicker fusion threshold even with the greater concentration. Although a previous review described this measure as being the most efficient psychometric test for detecting differences between treatment and control groups [7], the degree of sedation which has previously been detected by CFFT seems to have been much deeper than that produced by 15% MAC of isoflurane. For example, Griffiths [8] found that 5–15 mg of midazolam depressed CFFT, but these doses were too potent for the subject to complete a sufficient number of saccades for analysis of PSV. Instead, he used the number of successfully completed saccades per session and found these values agreed strikingly well with those provided by CFFT. We took the inverse measure (error %) and also found this to be an effective indicator of sedation.

When viewed as tests for different levels of recovery, the residual effects of isoflurane could be detected by PSV as long as 5 and 15 min after discontinuation of 30 min of administration of 10% and 15% MAC concentrations of isoflurane, respectively. CFFT and CRT failed to demonstrate any residual effect even 10 min after each concentration of isoflurane was discontinued. Amongst the three, only PSV was able to demonstrate the slower recovery after 15% MAC than after 10% MAC isoflurane. PSV thus proved to be the most sensitive of these tests for the detection of sedation.

Subjectively, however, the residual effects of isoflurane could be detected 10 min after 15% MAC of isoflurane. This agrees with McMenemin and Parbrook [13] who failed to demonstrate any residual effect 5 min after a 20-min inhalation of 0.4% isoflurane using three objective tests, while subjective assessment of physical and mental sedation using VAS persisted for 25 min after isoflurane.

In view of our findings, one should treat with caution the view of Rodrigo and Rosenquist [14] that patients were "street fit" 10 min after a 30-min administration of 0.5% isoflurane sedation for dental extractions. Their tests were clearly too insensitive to detect minor degrees of residual sedation. Whatever "street fit" implies in practice, the patients were unlikely to have recovered fully, even though residual depression was not detected.

Values of r^2 in excess of 0.9 were obtained for the regression of normalized CRT and CFFT on both the end-tidal concentration and calculated brain tension of isoflurane (table I). These measurements were taken only at near steady states. In contrast, the r^2 values obtained from regressing normalized PSV depression and error % on the end-tidal concentration were not as great, mainly because of the influence of measurements taken during early recovery when brain tension would not be in equilibrium with end-tidal concentration. When normalized PSV depression and error % were regressed on estimated brain tension, r^2 values were also about 0.9. Thus all the objective measures reflected the brain tension of isoflurane.

The r^2 values obtained from regressing the visual analogue scores were small whether end-tidal concentrations ($r^2 = 0.19$) or estimated brain tension ($r^2 = 0.51$) was used, confirming that subjective assessment reflects the brain tension of isoflurane less well than objective measures.

The results of this and a previous study [4] indicate that peak saccadic velocity is depressed in a dose-related fashion by 5% and 10% MAC concentrations of isoflurane, making it the most sensitive measure of sedation. At concentrations greater than 10% MAC it is a less precise measure because of a significant increase in the number of errors. The percentage of errors, however, then becomes a good indicator for assessing deeper levels of sedation. CRT is also a satisfactory measure at levels of sedation deeper than 10% MAC, but CFFT is not sensitive enough even at 15% MAC concentrations of isoflurane. This suggests that a potentially useful combination of indicators for following complete recovery from anaesthesia would be peak saccadic velocity, error % and choice reaction time.

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British Journal of Anaesthesia 1993; 71: 845–848

ANTIEMETIC EFFICACY OF PROPHYLACTIC ONDANSETRON IN LAPAROSCOPIC SURGERY: RANDOMIZED, DOUBLE-BLIND COMPARISON WITH METOCLOPRAMIDE

J. H. RAPHAEL AND A. C. NORTON

SUMMARY

In a randomized, double-blind study, we have compared the prophylactic antiemetic efficacy of ondansetron with that of metoclopramide in 123 patients undergoing general anaesthesia for day-case gynaecological laparoscopic surgery. The patients received either i.v. ondansetron 4 mg or metoclopramide 10 mg immediately before a standard anaesthetic. The number of patients with no nausea or vomiting in the ondansteron group was 50 (82%) compared with 29 (47%) in the metoclopramide group ($P < 0.001$*). In those patients with a previous history of postoperative nausea and vomiting, nausea was less severe in those receiving ondansetron compared with those receiving metoclopramide (*$P < 0.05$*). We conclude that preoperative prophylactic administration of i.v. ondansetron was superior to metoclopramide in preventing nausea and vomiting after general anaesthesia for day-case gynaecological laparoscopic surgery.* (Br. J. Anaesth. 1993; **71**: 845–848)

KEY WORDS

Pharmacology: metoclopramide, ondansetron. Vomiting: nausea. Surgery: gynaecological.

The incidence of nausea and vomiting after gynaecological laparoscopic surgery is particularly great, with previous studies reporting rates of around 50% [1–7]. The antiemetics commonly used at present (metoclopramide, prochlorperazine, droperidol and hyoscine) have limited efficacy on postoperative nausea and vomiting (PONV) after laparoscopy [1, 6, 7] and are associated with side effects such as sedation and extrapyramidal signs which may be important in day-case surgery [8–13].

Less commonly used antiemetic drugs (perphenazine, cyclizine, atropine, ginger root, acupuncture) and avoidance of nitrous oxide have not been shown to have consistent antiemetic efficacy [3, 7, 14, 15].

Ondansetron is a relatively new antiemetic agent that appears to show promise in this surgical procedure in studies comparing it with placebo [16–18]. In this study, we have compared the prophylactic antiemetic efficacy of ondansetron with metoclopramide in day-case gynaecological laparoscopic surgery.

PATIENTS AND METHODS

We studied patients undergoing elective day-case gynaecological laparoscopic surgery, with Local District Ethics Committee approval and informed patient consent. Patients who were pregnant, breast feeding, taking any medication other than the oral contraceptive pill or currently being treated for nausea or vomiting were excluded. The study was conducted in a double-blind manner with coded ampoules and restricted and stratified randomization was used, with sealed envelopes, to ensure treatment groups of the same size and an equal number of patients with previous PONV in each group.

Immediately before anaesthesia, patients were given either i.v. ondansetron 4 mg or metoclopramide 10 mg. Anaesthesia was induced with thiopentone 3.5–5 mg kg^{-1} and the trachea intubated after administration of suxamethonium 100 mg. Anaesthesia was maintained with 66% nitrous oxide and 1% isoflurane in oxygen, fentanyl 1.5 $\mu g\ kg^{-1}$, atropine 0.6 mg and additional suxamethonium up to 80 mg. Each anaesthetic was administered by one of three anaesthetists (two consultants and a registrar) and the surgery performed by one of two consultant gynaecologists.

Nausea and vomiting were assessed in all patients by the same observer immediately before operation and upon awakening, at 2 h and 4–6 h after operation. In addition, nausea and vomiting were assessed after hospital discharge up to 24 h after surgery, using a patient questionnaire.

Nausea was assessed by asking patients if they felt nauseated or sick, and was classified as mild or severe.

Both vomiting and retching were considered as emetic events. The nursing staff noted such events in hospital and after discharge the patients recorded these events on the questionnaire.

At each patient assessment, the degree of sedation was classified as asleep, drowsy or awake. Patients were questioned specifically about the presence of headache and asked to volunteer any other complaints. They were observed on these occasions for any evidence of extrapyramidal signs.

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After operation, antiemesis was provided by i.m. prochlorperazine 12.5 mg and analgesia by i.m. morphine 10 mg at the discretion of the nursing staff.

Statistical analysis

Patient data were analysed by *t* test, Mann–Whitney *U* test and chi-square test; other results were analysed by chi-square test, Fisher's exact test and Kruskal–Wallis one-way analysis of variance. Significance was taken at $P < 0.05$.

RESULTS

Sixty-one patients received ondansetron and 62 received metoclopramide. One patient was excluded from the study after randomization because additional atropine was administered during operation to correct a bradycardia.

There were no significant differences between the groups in age, body weight, previous history of PONV, history of motion sickness, grade of anaesthetist, duration of anaesthesia or administration of postoperative opioid drugs. More patients in the metoclopramide group were in the luteal phase of the menstrual cycle and more patients in the ondansetron group were menstruating, but neither of these differences was significant (table I).

One hundred and six patients (86 %) completed the questionnaire: 50 in the ondansetron group and 56 in the metoclopramide group. Of the patients who failed to complete the questionnaire, the proportion in each group with no nausea and vomiting in the first 6 h was similar to that found in those who did complete the questionnaire. None of the patients with a previous history of PONV failed to complete the questionnaire (table II).

Nausea and vomiting

The administration of postoperative antiemesis was considered as treatment failure and these patients were deemed to have experienced emesis.

The number of patients with no postoperative nausea and vomiting in the first 6 h after operation was 53 (87 %) in the ondansetron group and 37 (60 %) in the metoclopramide group ($P < 0.001$) (table III). Combining the data collected in hospital with those revealed by the questionnaire (tables II and III) revealed the number of patients with no PONV in the first 24 h after operation to be 50 (82 %) in the ondansetron group and 29 (47 %) in the metoclopramide group ($P < 0.001$). Of those who were nauseated during the first 6 h after operation, the worst degree of nausea was less in the ondansetron group, although this did not reach statistical significance ($P < 0.1$) (fig. 1). The incidence of PONV was smaller in the ondansetron group at all times; this difference was significant except for data at 2 h after operation (fig. 2).

In those patients with previous PONV, the severity of nausea was less in those given ondansetron than in those given metoclopramide ($P < 0.05$) (fig. 3).

Side effects

There was no significant difference between the groups in the time to awakening (table I) or sedation at 2 h and 4–6 h.

TABLE I. *Patient characteristics and anaesthetic data (median (range), mean* (SD) *or No. patients)*

	Ondansetron ($n = 61$)	Metoclopramide ($n = 62$)
Age (yr)	35 (16–44)	33 (23–57)
Weight (kg)	68.0 (12.1)	67.3 (9.3)
Previous PONV	14	14
Motion sickness	9	10
Junior anaesthetist	28	25
Menstruating	16	8
Luteal phase	10	18
Anaesthetic duration (min)	14.0 (3.8)	13.6 (3.4)
Postop. morphine	10	8
Recovery time (min)	8.2 (1.8)	8.6 (2.0)

TABLE II. *Results from the questionnaire on emesis (nausea and vomiting) after hospital discharge between 6 and 24 h after operation*

	Ondansetron ($n = 61$)	Metoclopramide ($n = 62$)
Number of replies	50	56
Emesis after discharge	6	22
Emesis after discharge; no emesis in hospital	3	8

TABLE III. *Comparison of the incidence of emesis (nausea and vomiting) in both treatment groups and in the subgroups with a previous history of PONV, in the first 6 h after operation.* $^{**}P < 0.001$ *compared with metoclopramide*

	Emesis	No emesis
Ondansetron group ($n = 61$)	8	53**
Metoclopramide group ($n = 62$)	25	37
Ondansetron group with previous PONV ($n = 14$)	5	9
Metoclopramide group with previous PONV ($n = 14$)	10	4

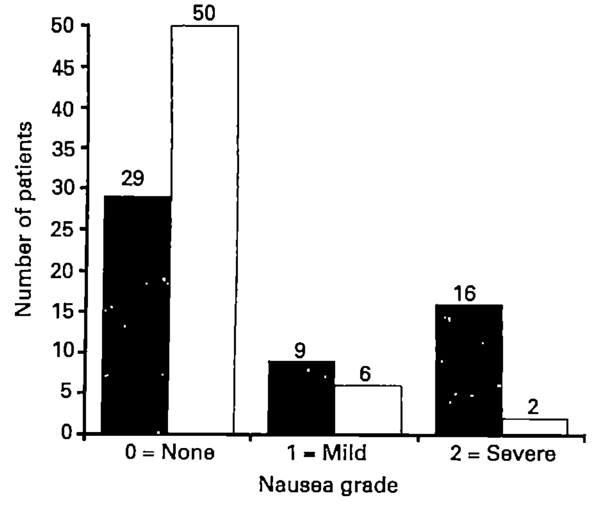

FIG. 1. Number of patients given metoclopramide (■) or ondansetron (□) who experienced nausea in the 6 h after operation.

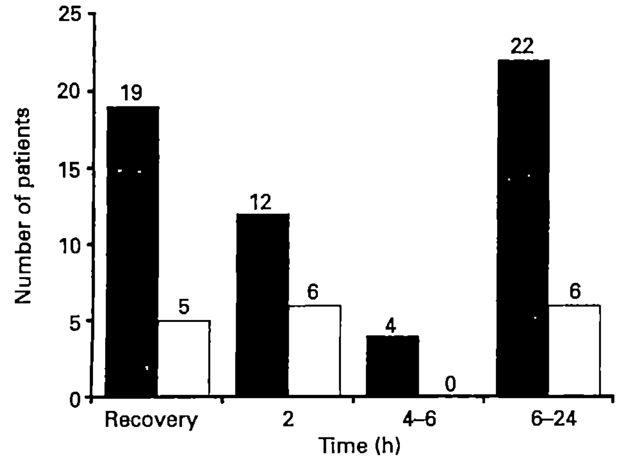

FIG. 2. Number of patients given metoclopramide (■) or ondansetron (□) who experienced emetic events within the defined time bands. Significance of differences between groups: recovery, $P < 0.01$; 2 h, $P > 0.1$; 4–6 h, $P < 0.05$; 6–24 h, $P < 0.001$.

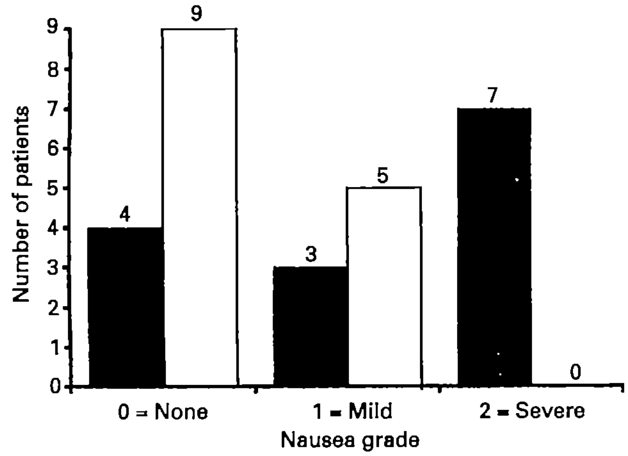

FIG. 3. Number of patients with previous PONV given metoclopramide (■) or ondansetron (□) who experienced nausea.

In the ondansetron group, headache occurred in two patients, urticaria at the injection site in one and a short-lived flush phenomenon in another. No other adverse effects were observed in this group. In the metoclopramide group, four patients reported headache, two complained of dizziness and two were noted to be restless.

DISCUSSION

The incidence of nausea and vomiting in the group that received metoclopramide (53%) was similar to that reported by others. In studies of patients having laparoscopic surgery alone or major gynaecological surgery that included laparoscopy, the incidence of nausea and vomiting after receiving metoclopramide is 30–60% [1, 6, 7].

There was less nausea and vomiting in the group receiving ondansetron. This difference was significant after awakening from anaesthesia and between 4 and 24 h after operation, but did not reach statistical significance at 2 h after operation.

In patients with previous PONV, there was a significant reduction in the degree of nausea in the group given ondansetron; however, the power of the study was insufficient to demonstrate any significant difference in the incidence of nausea and vomiting.

There was no significant difference between the two groups in time to awakening and sedation and there were no serious side effects recorded in each group.

The anaesthetic technique used in this study may differ from others. The anaesthetists involved in this study use thiopentone rather than propofol because patients remain in hospital for 6 h after laparoscopic surgery; there have been no problems with delayed hospital discharge. Various studies have demonstrated a smaller incidence of emesis associated with a propofol infusion technique compared with thiopentone and inhalation agents [19].

Intermittent suxamethonium was used to allow controlled ventilation because the median time of operation was short (14 min in this study). Although this technique is uncommon in day-case surgery, it may result in less emesis than is associated with the use of non-depolarizing neuromuscular blocking drugs, by avoiding the requirement for the antagonism of neuromuscular block with neostigmine [20].

Postoperative pain is associated with nausea and vomiting, but the relief of pain by appropriate doses of opioids results in less nausea [21]. We did not use non-steroidal anti-inflammatory agents in addition to opioids as the incidence and severity of postoperative pain appeared acceptable with an intraoperative opioid alone.

Nausea and vomiting are common unpleasant experiences associated with surgery which, on occasions, may lead to delayed discharge and even unexpected hospital admission for day-cases. The incidence of nausea and vomiting is particularly great with laparoscopic surgery [1–7]. The antiemetics used commonly at present (droperidol, prochlorperazine and metoclopramide) have limited efficacy and are associated with a variety of side effects. Droperidol appears to be the most effective, but is associated with a relatively large incidence of extrapyramidal symptoms [8, 9]. There is only limited information on the efficacy of prochlorperazine in day-case surgery and there are data to suggest that there may be a greater incidence of extrapyramidal effects with prochlorperazine than with metoclopramide [22]. Although i.v. metoclopramide appears to have little effect in preventing PONV after gynaecological surgery, we elected to compare it with i.v. ondansetron because the former is administered commonly by this route in day-case anaesthetic practice.

We have demonstrated that i.v. ondansteron was superior to i.v. metoclopramide as a prophylactic antiemetic in gynaecological laparoscopy. Those patients with previous PONV are important to consider because of their greater susceptibility to emesis [23]. They are both clinically and economically an important group to target, as the widespread prophylactic use of an expensive antiemetic may be difficult to justify. Although this study showed a reduction in the degree of nausea suffered by patients with previous PONV given ondansetron, it was of insufficient power to determine if ondansetron significantly attenuated nausea and vomiting in this subgroup of patients.

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EFFECT OF THIOPENTONE ON MOTOR EVOKED POTENTIALS INDUCED BY TRANSCRANIAL MAGNETIC STIMULATION IN HUMANS

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SUMMARY

We have studied the effect of repeated doses of thiopentone on motor evoked potentials (MEP) after transcranial magnetic stimulation in 13 patients. Thiopentone was administered i.v. in an initial dose of 2 mg kg^{-1}, followed by repeated doses (1 mg kg^{-1} every 3 min) until the appearance of burst suppression on the EEG. The total dose administered was mean 10.7 (SD 2.6) mg kg^{-1}. The magnetic coil was placed over the MEP scalp stimulation region and evoked electromyographic responses were recorded from the contralateral abductor pollicis brevis. After an initial dose of thiopentone, reproducible MEP responses were recorded in all patients, but amplitudes were reduced to 42.8% of baseline values. Further administration of repeated doses of thiopentone produced a dose-dependent decrease in success rate of MEP recordings and a significant reduction in MEP amplitude ($P < 0.01$). Latency did not change significantly, although there was a tendency to increase. During burst suppression on the EEG, MEP was not recorded successfully in all patients. We conclude that MEP recording during the administration of thiopentone is feasible only at a minimum dose, with a marked reduction in MEP amplitude. (Br. J. Anaesth. 1993; **71**: 849–853)

KEY WORDS

Anaesthetics, intravenous: thiopentone. Brain: electroencephalography, evoked potentials.

Transcranial electrical and magnetic stimulation to produce motor evoked potentials (MEP) has been advocated to assess the functional integrity of motor pathways during anaesthesia [1–3]. High voltage electrical stimuli are assumed to excite the pyramidal cells directly beneath their cell bodies, whereas magnetic stimuli probably excite the descending motor pathways transsynaptically [4, 5]. Both techniques make it possible to evoke motor responses in various muscles of the upper and lower limbs and of the face. However, anaesthetic agents may interfere with the reproducibility of such responses and limit the usefulness of this technique [3, 6–8].

Thiopentone is a commonly used anaesthetic agent which reduces cerebral blood volume and may protect the brain in large doses. Patients with severe head injury, increased intracranial pressure, brain swelling and massive cerebral ischaemia have been treated with large doses of barbiturate [9–11]. In such patients, it is crucial to assess the descending pathways in addition to ascending pathways, using somatosensory evoked potentials (SEP).

Several authors have demonstrated the effects of thiopentone on SEP and MEP [7, 8, 12–16], but there are no data on the minimum dose of thiopentone for successful recording of MEP during high-dose barbiturate therapy. Therefore, we have evaluated the effect of thiopentone on MEP induced by transcranial magnetic stimulation.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of Osaka Neurological Institute and informed consent was obtained from each patient. We studied 13 patients (mean age 40.2 yr (range 19–65 yr), ASA I–II; nine women) undergoing elective surgery. All patients were free from motor dysfunction and had normal MEP responses at the preoperative examination. Patients with liver dysfunction or heart disease were excluded. Each patient was premedicated i.m. with atropine 0.5 mg and famotidine 20 mg 30 min before induction of anaesthesia. An i.v. catheter was inserted and the overnight fluid deficit was replaced with glucose-free lactated Ringer's solution. Routine monitoring included ECG, automated oscillotonometry, pulse oximeter, temperature and end-tidal carbon dioxide measurements.

The motor cortex and cervical region (7th cervical vertebra) were stimulated with a magnetic stimulator (SMN-1100, Nihon Kohden, Japan), consisting of a capacitor and a flat coil (i.d. 10.5 cm; o.d. 17 cm). A large current (7500 A) passes through the coil after discharge of the capacitor (1500 μF). The strength of the magnetic fields varies according to the electric

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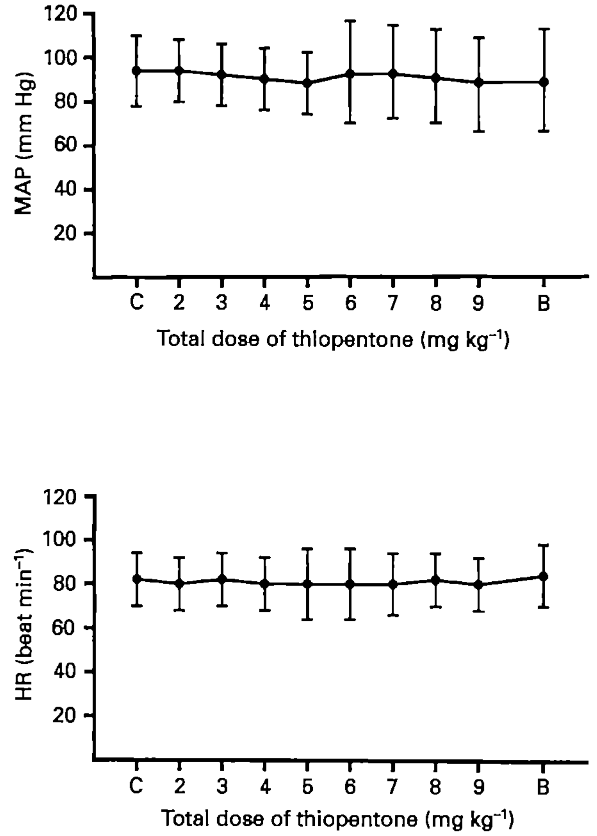

FIG. 1. Changes in mean arterial pressure and heart rate during administration of repeated doses of thiopentone (mean, SD). C = Control; B = burst.

current, which is controlled by the voltage of the discharge current of the capacitor. The maximum magnetic field of 0.4 Tesla was obtained with an output voltage of 1000 V (= 7500 A) about 166 μs after the onset of discharge. Magnetic stimulation was given with a stimulus intensity of 900 V for the motor cortex and 600 V for the cervical region. MEP were recorded with surface electrodes placed over the abductor pollicis brevis muscle. Signals were amplified and recorded with the restricted filter setting of 20–3000 Hz, using a conventional electromyographic recording system (Neuromatic 2000C, Dantec, Denmark). MEP amplitude was measured as the vertical distance between two successive peaks and onset latency was measured on the MEP of shortest latency. EEG was recorded using a Neurofax (Nihon Kohden, Japan). Gold cup electrodes were placed according to the international 10–20 system at F_3, F_4, P_3, P_4, O_1, O_2 references to linked earlobes. A time constant of 0.3 s and a high-pass filter of 120 Hz were used. Electrode impedances were matched within 1 kΩ.

After duplicate baseline recordings of MEP were obtained, thiopentone was given i.v. in an initial dose of 2 mg kg^{-1}, followed by repeated doses (1 mg kg^{-1}) every 3 min until the appearance of burst suppression on the EEG. Each dose was given over 10 s. MEP induced by transcranial magnetic stimulation were recorded 2 min after the injection of each dose of thiopentone. MEP induced by magnetic stimulation of the cervical region were recorded before and after administration of the total doses required for appearance of burst suppression. At 1-min intervals during the study, arterial pressure and heart rate were recorded and methoxamine was administered if necessary for maintenance of arterial pressure. Ventilation was assisted manually using a facemask with 100 % oxygen to maintain an end-tidal carbon dioxide partial pressure of 4.6–5.3 kPa. All patients had a rectal temperature > 36.5 °C. At the conclusion of the study, the patients were given vecuronium 8 mg i.v. and the trachea was intubated.

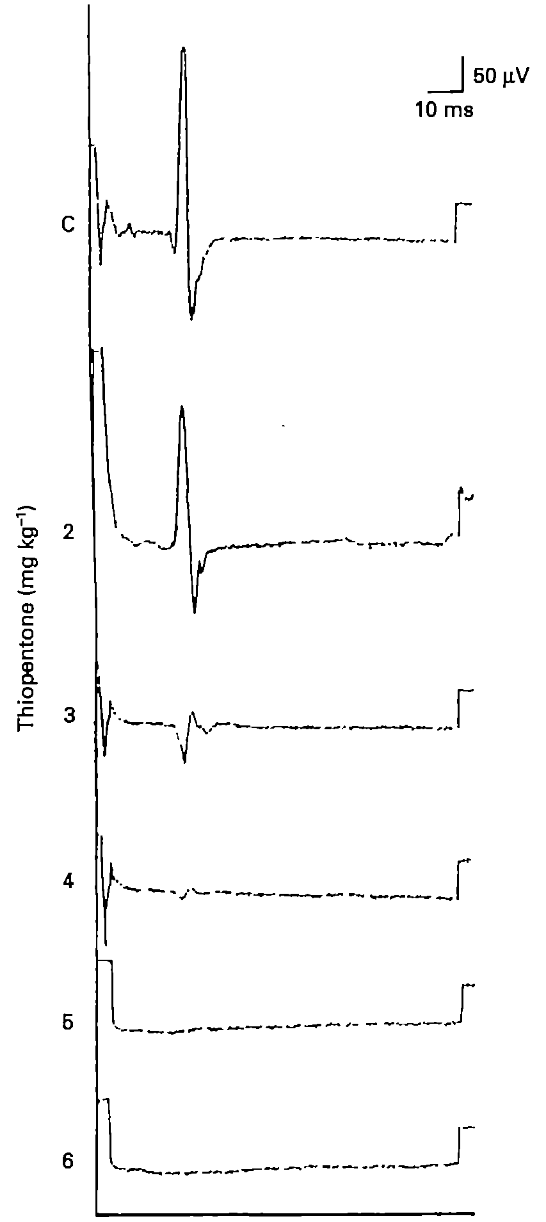

FIG. 2. Motor evoked potentials induced by transcranial magnetic stimulation before and during the administration of repeated doses of thiopentone. C = Control.

Data were analysed using a one-way analysis of variance (ANOVA) with repeated measures and Tukey's post hoc test. Statistical significance was assumed at $P < 0.05$.

RESULTS

In all patients, we obtained distinct baseline MEP induced by transcranial magnetic stimulation. Latencies and amplitudes were 21.1 (0.5) ms and

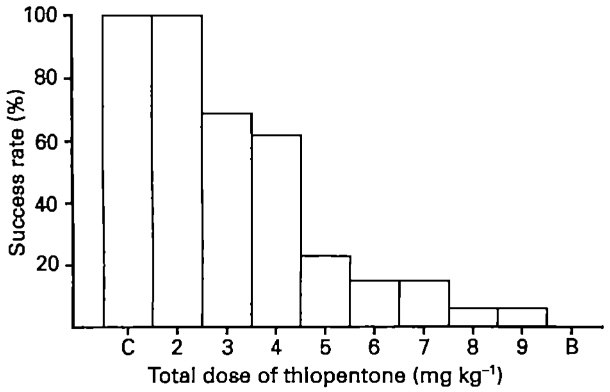

FIG. 3. Success rate of motor evoked potentials induced by transcranial magnetic stimulation during the administration of repeated doses of thiopentone. C = Control; B = burst.

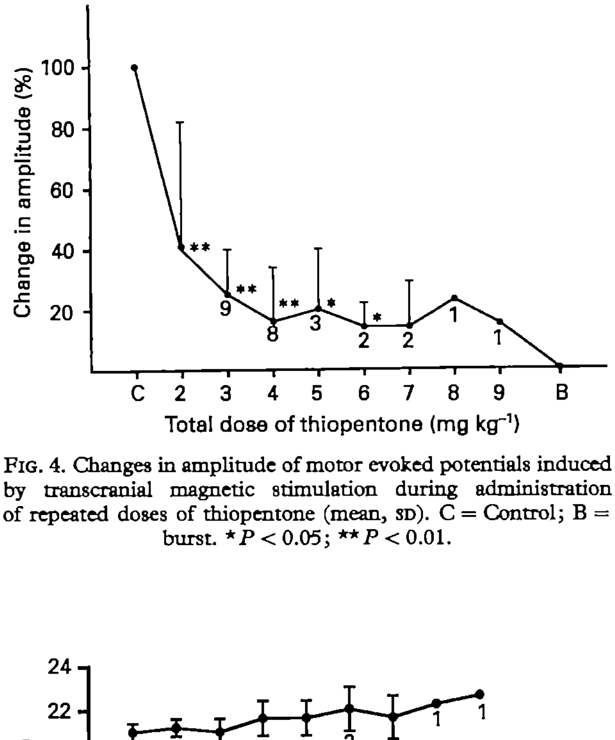

FIG. 4. Changes in amplitude of motor evoked potentials induced by transcranial magnetic stimulation during administration of repeated doses of thiopentone (mean, SD). C = Control; B = burst. $*P < 0.05$; $**P < 0.01$.

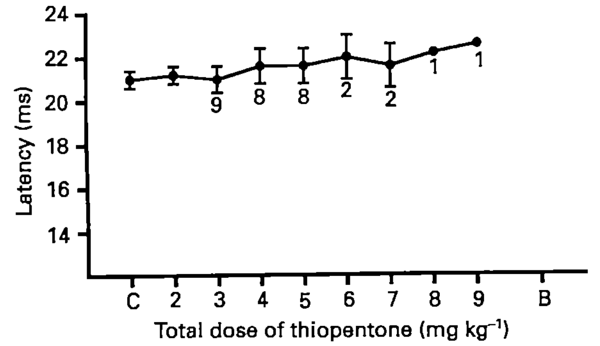

FIG. 5. Changes in latency of motor evoked potentials induced by transcranial magnetic stimulation during administration of repeated doses of thiopentone (mean, SD). C = Control; B = burst.

1069.4 (968.0) µV, respectively. The total dose of thiopentone administered was 10.7 (2.6) mg kg^{-1}. Mean arterial pressure and heart rate did not change significantly during the study (fig. 1).

Figure 2 shows MEP recordings before and during the administration of thiopentone and figures 3 and 4 show the success rate of MEP recordings and changes in MEP amplitudes during administration of thiopentone. After an initial dose of thiopentone 2 mg kg^{-1}, reproducible MEP responses were recorded in all patients, but amplitudes were reduced to 42.8 % (range 0.75–85 %) ($P < 0.01$). With thiopentone 3 mg kg^{-1}, MEP responses were obtained in nine of 13 patients and amplitudes ranged from 7.5 to 57 % (average 24.4 %) ($P < 0.01$) of the baseline values. With thiopentone 4 mg kg^{-1}, MEP responses were obtained in eight patients, with amplitudes reduced to 16.4 % ($P < 0.01$). MEP response was obtained until a total dose of thiopentone 9 mg kg^{-1} had been given to one patient. No MEP were obtained during burst suppression of the EEG.

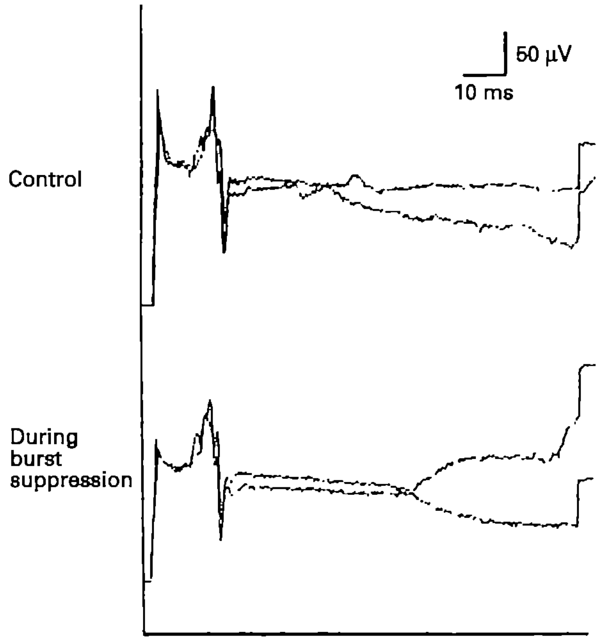

FIG. 6. Motor evoked potentials induced by magnetic stimulation of the cervical region before and during the administration of thiopentone (burst suppression).

There were no significant changes in MEP latency during administration of thiopentone (fig. 5).

Amplitudes and latencies of MEP induced by magnetic stimulation of the cervical region did not change significantly after administration of thiopentone (amplitude 740.8 (712.1) µV before and 710.3 (702.8) µV after thiopentone; latency 12.2 (1.0) ms before and 12.3 (0.8) ms after thiopentone) (fig. 6).

DISCUSSION

Our results showed that MEP responses induced by transcranial magnetic stimulation were obtained during administration of thiopentone 2 mg kg^{-1} with a marked reduction in MEP amplitudes. Further administration of repeated doses of thiopentone induced a dose-dependent decrease in the success rate of recording MEP and MEP amplitudes. MEP latencies did not change significantly, although there was a trend to increase. The amplitudes and latencies of MEP induced by magnetic stimulation of the cervical region did not change significantly during administration of thiopentone.

The results of our study are consistent with previous studies. Zentner, Kiss and Ebner [7] demonstrated that an i.v. bolus of thiopentone 250 mg induced a marked reduction in amplitude of MEP by transcranial electrical stimulation in comatose patients. Nadstawek Taniguchi and Bremer [8] demonstrated that MEP elicited by transmagnetic stimulation disappeared completely during continuous infusion of thiopentone producing very light anaesthesia in 12 of 15 patients. In the present study MEP recording during administration of thiopentone was feasible only with a minimum dose.

The effect of thiopentone on MEP was similar to that described for SEP [12–16]. Sloan, Kimovec and Serpico [12] demonstrated that a bolus of thiopentone 4 mg kg^{-1} induced a significant increase in latency with a decrease in amplitude of the early cortical response to median nerve stimulation. Abrahamian and colleagues [13] recorded the cortical response to median nerve stimulation in surgical patients and observed that incremental administration of thiopentone 6–8 mg kg^{-1} occasionally produced increases in the latency of the primary specific complex. Drummond, Todd and U [14] demonstrated that the administration of a dose of thiopentone in excess of twice that required to produce EEG isoelectricity caused dose-related increases in latency, with significant reductions in amplitudes of the cortical primary specific complex.

The mechanism of the effect of thiopentone on MEP induced by transcranial magnetic stimulation is not clear; however, it may be related to the inhibitory action of thiopentone on synaptic transmission in the central nervous system. Magnetic fields induced for MEP recordings presumably activate preferentially the transsynaptically-mediated cortical motoneurones, producing mainly indirect (I) waves [5].

We observed great variability in the doses of thiopentone which affected monitoring of MEP. The causes are not clear, but several possible explanations may be advanced. Great variability in amplitudes of MEP have been reported between subjects [1] and this may have influenced our results. The concentration of thiopentone at sites of action in the brain may vary markedly between subjects and several authors have observed the great variability in the dose of thiopentone required to produce suppression [17, 18].

One possible criticism of our study is the use of repeated doses of thiopentone. In a preliminary study, we administered thiopentone 4 mg kg^{-1}, but we could not record MEP in some patients. Therefore, we chose to use repeated doses with an initial dose of 2 mg kg^{-1} to identify the minimum for successful recordings of MEP. After a single i.v. dose of thiopentone, unconsciousness occurs after 10–20 s and the depth of anaesthesia may increase for up to 40 s and then decrease progressively until consciousness returns in 20–30 min [19]. Moffat and Wollmen [20] demonstrated that EEG changes occurred during a 3-min period when the drug was administered, were evident 2 min later and had disappeared by 5–10 min after the administration of thiopentone was completed. Therefore, we measured MEP responses 2 min after administration of each dose of thiopentone at 3-min intervals. However, the effects of thiopentone on MEP may differ according to whether a fixed dose of thiopentone is administered in the form of a bolus or by several increments.

The magnetic stimulator used in the present study has a maximum magnetic field of 0.4 Tesla, which is somewhat less than that of other stimulators [1] and may influence the results obtained in the present study. A greater magnetic field may increase the success rate of recording MEP.

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BLOOD LOSS DURING REPAIR OF CRANIOSYNOSTOSIS

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SUMMARY

Surgical repair of craniosynostosis carries a high risk with large blood losses. Over a 2-yr period, we have managed 115 patients undergoing craniosynostosis repair with peroperative haemodilution to achieve a final PCV of 0.28–0.35. Measurements of PCV allowed calculation of estimated blood losses and transfused volumes in terms of red blood cell mass. Total estimated red cell volume lost was 91±66% of patient's estimated red blood cell volume during the peroperative period. The type of skull deformation and surgical procedure determined the extent of peroperative bleeding. Peroperative transfusion was satisfactory in 48% of patients and slight overtransfusion was noted in 32%. During the postoperative period, liberal administration of blood led to overtransfusion and possibly unnecessary transfusion in 74% of patients. Because of the well known risks of transmission of infectious disease, strict volume compensation with development of haemodilution and autotransfusion procedures should be used to limit these risks. (Br. J. Anaesth. 1993; **71**: 854–857)

KEY WORDS

Blood: loss, transfusion. Surgery: paediatric neurosurgery.

Premature closure of skull sutures is a relatively common disorder, with an estimated incidence of 1 per 1000 births [1, 2]. In the absence of early surgical correction, compensatory deformation of the skull occurs during rapid growth of the brain in early infancy and this may lead to increased intracranial pressure, especially in children aged more than 1 yr, particularly when multiple sutures are involved [3]. With single suture involvement (the most frequent situation), effects on brain development are variable and there are mostly cosmetic problems [3, 4]. The goal of surgery is to restore normal anatomy at an early age in order to achieve the best cosmetic result and avoid possible cerebral consequences [1, 5]. Surgical procedures for correction of craniosynostosis are performed, therefore, in young infants with a small blood volume and represent major craniofacial surgery with unavoidable and extensive blood loss. Accurate determination and precise restoration of blood losses are important during and after operation. Kearney, Rosales and Howes [6] described an elegant method of assessing peroperative blood loss in this type of procedure. The aim of this study was to evaluate blood loss and adequacy of transfusion practices in a large series of patients undergoing primary correction of craniosynostosis.

PATIENTS AND METHODS

After obtaining parents' consent and Institutional Board approval, from January 1988 to January 1990 we studied patients undergoing correction of craniosynostosis. A note was made of age and weight at operation, perinatal history, type of craniosynostosis and associated anomalies or dysmorphic syndromes, type of surgical procedures performed, duration of surgery, peroperative monitoring, peroperative complications and duration of assisted ventilation after operation. The surgical procedure depended upon the type of synostosis and the age of the patient. Strip craniectomies, often with associated posterior craniectomy, were the most simple procedures used only in very young children with isolated sagittal suture involvement (scaphocephaly); other procedures included forehead reconstruction, floating forehead and complex vault remodelling. All the procedures were performed under general anaesthesia without induced hypotension after skull infiltration with adrenaline 1:200000 in normal saline.

Anaesthesia was maintained using continuous i.v. infusion of alfentanil and controlled ventilation with 0.8–1.5% isoflurane and 50% nitrous oxide in oxygen. Monitoring included continuous ECG, core temperature, non-invasive automated arterial pressure and end-tidal carbon dioxide analysis. Invasive monitoring (arterial or central venous pressure) was used if necessary. Preoperative blood samples were obtained for red blood cell and platelet count, measurement of haemoglobin and PCV and coagulation screen. Serial blood samples were obtained 2-hourly during operation and 12 h after operation and as frequently as clinically indicated, for measurement of blood-gas tensions and PCV.

Intraoperative management included strict observance of an isovolaemic haemodilution regimen,

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TABLE I. *Nature of skull deformations, and surgical procedures*

Type of skull deformation		Surgical procedures	
Scaphocephaly	49 (43 %)	Forehead reconstruction	57 (50 %)
Plagiocephaly	21 (18 %)		
Trigonocephaly	10 (9 %)	Strip craniectomy	31 (27 %)
Oxycephaly	9 (8 %)		
Brachycephaly		Floating forehead	18 (15 %)
Isolated	10 (9 %)		
Crouzon syndrome	6 (5 %)	Complex	9 (8 %)
Apert syndrome	5 (4 %)		
Complex	5 (4 %)		

with fluid replacement, based upon haemodynamic variables and comprising human serum albumin and packed red blood cells in order to maintain PCV in the range 0.28–0.35—a value considered generally as adequate for oxygen transport and tissue delivery [7]. Fresh frozen plasma was used only in patients requiring more than 70 % of estimated blood volume transfusion.

At the end of surgery, anaesthesia was discontinued and the trachea extubated or the patient sedated lightly with assisted ventilation. The criteria used for extubation were: rapid recovery with stable spontaneous ventilation, haemodynamic stability and normothermia, short-duration procedure with relatively small blood loss and absence of continuing bleeding via surgical drains. Patients were observed closely for at least 12 h. Full blood cell count and coagulation screen were obtained in the postoperative period in all patients. The type, volume and timing of transfused blood products were noted. In an attempt to simplify estimation of blood loss, all estimated volumes referred to red cell volumes; fresh frozen plasma volumes were analysed separately. Estimated body blood volume (EBV) = 80 ml kg^{-1} and red cell volume (ERCV) = EBV × PCV were calculated before operation.

The following variables were then calculated for the periods during and after operation: estimated red cell volume transfused (RCT) = 0.75 × volume of packed red cells; estimated red cell volume deficit (ERCD) = ERCV × PCV variation; estimated red cell volume lost (ERCL) = ERCD + RCT; percent of ERCV lost = ERCL/ERCV.

Data were statistically analysed using the Statistical Package for the Social Sciences (SPSS/PC+, MJ Norusis Ed. SPSS Inc. Chicago 1992). Tabular data were analysed using contingency tables (chi-square or Fischer's exact test) and differences of means using Student's *t* test, ANOVA or Kruskal–Wallis, as appropriate, depending on distribution and number of variables. Statistical significance was assumed with $P < 0.05$.

RESULTS

In a 2-yr period, we studied 130 patients treated by two surgeons; 15 were subsequently eliminated from analysis because of inadequate data. All patients had primary craniosynostosis repair, mean age at operation was 11.6 months (range 1–154 months; 77.3 % of the population less than 12 months old) and mean body weight 8.63 kg (range 4–44 kg; 70.4 % less than 10 kg). The type of skull deformation and surgical procedure are shown in table I. As in other series, isolated sagittal synostosis resulting in scaphocephaly was the most common type, representing 42.6 % of cases [2].

Invasive monitoring was used in 70 patients (60 %), arterial cannula alone in 47, central venous catheter alone in three and both arterial and central venous monitoring in 20 patients. Ninety percent of the patients had arterial cannulae during the last year of the study. Duration of surgery differed significantly between surgical procedures, with a mean of 79.4 (SD 33.9) min for strip craniectomies and 137 (41.4) min for more complex procedures. Total estimated red blood cell volume lost during the peroperative period was 91 (66) % of preoperative estimated red cell volume (range 5–400 %). ERCV, RCT, ERCD, ERCL and percent of ERCV lost are presented in table II. Only 13 patients (11.3 %) undergoing simple surgical procedures did not require peroperative blood transfusion.

All other children (88.7 %) had intraoperative transfusion with a mean 243.8 (181.4) ml (range 50–900 ml) of packed red blood cells. Fresh frozen plasma was used in only 56 children (48.7 %). According to our criteria, 48.7 % of the patients were adequately transfused, 32 % were slightly overtransfused and 19 % were undertransfused. One patient died during surgery after massive bleeding from a large venous sinus. Venous air embolism occurred in three patients (2.6 % incidence), without further consequences. Transient hypotension was the most frequent peroperative incident, with a 35 % incidence. At the end of surgery, the trachea was extubated in 68.5 % of children.

The determinant factors for postoperative assisted ventilation were peroperative blood loss and duration of surgery. Duration of postoperative ventilation was 40–540 min. In the first 24 h after surgery, a mean 232.13 (148.8) ml of blood was lost through surgical drains (table II). The PCV in drainage fluid was, in most instances, less than 0.15. Overtransfusion, according to our criteria, was more frequent in the postoperative period than during surgery (74 % *vs* 32 % ($P < 0.001$)), leading to possible unnecessary transfusion in some patients.

Postoperative complications included transient hypotension in 15 % of patients, persistent bleeding in excess of 50 % of estimated red cell volume in 12.6 % and thrombocytopenia (platelet count less than 65 000 ml^{-1}) in three patients. Postoperative haemostasis was judged satisfactory with an activated

TABLE II. *Mean* (SD) *blood loss during the study. ERCL = estimated red cell volume loss; RCT = packed red cell volume transfused; ERCL/ERCV = % of patient's estimated red cell volume lost; ERCD = final red cell volume deficit. †Negative value indicates postoperative overtransfusion*

	During op.	After op.	Total
ERCL (ml)	191.5 (124.63)	52.75 (80.28)	240.72 (146.09)
RCT (ml)	182.87 (136.48)	89.85 (82.82)	272.72 (137.6)
ERCL/ERCV (%)	91 (65.9)	27.4 (42.3)	118.2 (86.1)
ERCD (ml)	6.15 (41.83)	−37.88 (48.14)†	−32 (42.2)

TABLE III. *Mean* (SD) *percentage of patient's estimated red cell volume lost and type of skull deformation. †Negative value indicates postoperative overtransfusion*

Type of synostosis	During op.	After op.	Total
Oxycephaly	49.1 (22.9)	−3.7 (16.8)†	45.4 (36.9)
Plagiocephaly	59 (37.4)	27.7 (41.7)	86.7 (56.2)
Trigonocephaly	92.4 (49.7)	11.7 (16.6)	104.1 (49.2)
Brachycephaly	105.3 (48.45)	25.5 (56.5)	130.9 (69.1)
Scaphocephaly	92.1 (65.2)	35.9 (38.4)	121.7 (78.2)
Complex	198.5 (165)	44.5 (97.6)	243.1 (259.4)

prothrombin time of 60% or more of the normal value in all patients. No change in PCV was noted 24 h after surgery; no further transfusion was required and PCV at discharge from the hospital was always 0.30 or more.

The age of the patient correlated highly with blood loss (99 (73)% of ERCBV lost in patients younger than 6 months, compared with 72 (38)% lost in patients older than 6 months ($P < 0.008$)). The type of skull deformation correlated with the percentage of estimated red cell volume lost during surgery ($P < 0.0001$) and there was a correlation between type of surgical procedure and peroperative ($P < 0.012$), but not postoperative, blood loss (table III). Separate analysis of the correlation between blood loss and type of surgical procedure was performed in the subgroup of scaphocephaly, for which three types of procedures could be used. Strip craniectomies involved less blood loss (60 (24.5)% of ERCV lost) than forehead reconstruction (106.4 (53.7)%) and complex vault remodelling (170.6 (10.3)%) ($P < 0.006$).

DISCUSSION

Craniofacial surgery for craniosynostosis treatment includes extensive osteotomies with considerable blood loss [2, 5, 6, 8–12]. Because of the well known complications of blood transfusion, with a current incidence of about 1 per 40000 and 5–10% of transfusion recipients being at risk of AIDS and hepatitis [13, 14], methods designed to reduce blood loss are of interest.

Induced hypotension has been used in the past without clear benefit [10]. Skin infiltration with vasoconstrictors is used frequently, but is not very effective because periosteum and bone, not the scalp, are the major sources of blood loss [8]. Acute normovolaemic haemodilution is now used routinely in many paediatric surgical procedures [7], but not, to our knowledge, during craniosynostosis surgery.

In this study, using strict guidelines for transfusion, we found no complications. However, it must be noted that about 10% of the patients could be satisfactorily managed without any packed red cell transfusion. Acute haemodilution alone is probably insufficient to avoid blood transfusion in this type of surgery and other techniques designed to reduce the need for homologous transfusion should probably be considered. Because of the small blood volume of young children, autologous transfusion with preoperative blood withdrawal is clearly not adequate to provide blood requirements during surgery. Peroperative blood salvage and retransfusion have been reported anecdotally during craniosynostosis repair [15]. In our recent experience with peroperative use of a cell saver in 15 patients, in spite of satisfactory blood salvage and significant reduction in homologous transfusion requirements, abrupt haemorrhage in patients with a small blood volume required associated use of homologous transfusion in nine patients.

The factors influencing peroperative blood loss have been analysed previously. In this type of surgery, trapping of large blood volumes in surgical drapes and dilution with irrigating fluids prevent precise measurement of blood loss. There are few published estimates of blood loss during these procedures; most refer to weighing sponges and measurement of suction volume [2, 8–10]. Kearney, Rosales and Howes reported an interesting method of assessing blood loss by serial determinations of PCV and calculation of red cell volume deficit. This method allows more precise evaluation of changes in blood volume and assessment of adequacy of transfusion practices [6]. Our blood losses were slightly greater than the reported values of 20–40% of estimated blood volume lost [6, 9–11] and may be explained partly by differences in surgical procedures, those in our series being more complex.

Forehead reconstructions and craniectomies with posterior flaps are associated with significantly more blood loss than strip craniectomies. As in other reports, we found that strip craniectomies had the smallest estimated blood loss. Because of the lack of details on surgical techniques in other series [6, 8–10] and the changes in surgical practice over a 15-yr period [6], comparisons are difficult. However, it is easier to compare our study with the report from the Children's Hospital at Denver, where extensive craniectomies and complex vault reconstruction represent the third most common neurosurgical procedure performed in infancy [5]. Our results were broadly comparable to those reported in that study [5], especially for brachycephaly and plagiocephaly treated with forehead reconstruction.

The duration of surgery varied between different types of skull deformation and different surgical procedures. It did not influence significantly the extent of operative blood loss. In these procedures, 20–50 % of the patient's estimated red cell volume may be lost in less than 30 min. For complex procedures the mean duration was similar to that of another series [6], but less than the duration observed by Loftness, Albin and O'Donnell [5]. The age of patients at the time of surgery was associated with blood loss, with a greater percentage of ERBCV lost in infants younger than 6 months. However, it must be noted that cosmetic and neurological outcome are more important in this age group [5, 6]. In our institution, the optimal age for surgery represents a compromise between surgical conditions with easier and shorter operations in younger children, and physiological tolerance to acute blood loss with greater haemodynamic stability in children older than 6 months. Thus most of our children were aged 6–12 months, with body weight 6–10 kg.

It appeared that postoperative management did not achieve the goal of controlled haemodilution and attempts to modify transfusion practice during the recovery period are now in place. This difference in management during and after operation, with possibly unnecessary transfusion during the postoperative period, was noted also by Kearney, Rosales and Howes, who did not use deliberate peroperative haemodilution [6]. This demonstrates clearly the inadequacy of transfusion regimens dealing more with measurement of blood drainage than with physiological observation and measurement of PCV. Another shortcoming of postoperative management in this study was the difficulty in establishing correlations between estimated blood losses and their principal determinants. There were no statistical correlations between estimated postoperative blood loss and determinants such as type of synostosis and surgical procedure.

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POSTOPERATIVE MULTIPLE ORGAN DYSFUNCTION SYNDROME ASSOCIATED WITH GUT MUCOSAL HYPOPERFUSION, INCREASED NEUTROPHIL DEGRANULATION AND C1-ESTERASE INHIBITOR DEPLETION

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SUMMARY

We have examined the relationship between gut mucosal perfusion, as determined by gastric intramucosal pH (pHi), changes in plasma neutrophil elastase concentrations and components of the contact system during elective major surgery and related these findings to patient outcome. Of the 26 patients studied, 16 developed gut mucosal hypoperfusion (pHi < 7.32*) by the end of surgery; four of these developed multiple organ dysfunction syndrome; three of these died. In this group there was a significant increase in neutrophil elastase (*$P < 0.005$*) and significant reductions in plasma components of the contact system from immediately before surgery to 24 h later. Ten patients maintained gut mucosal perfusion (pHi* $\geqslant 7.32$*); none of these developed life threatening complications. In this group there was no significant increase in neutrophil elastase and, although there were significant reductions in some plasma components of the contact system, concentrations of C1-esterase inhibitor (the main inhibitor of the contact system) were not significantly reduced. We conclude that gut mucosal hypoperfusion, neutrophil degranulation and activation of the contact system to the extent that C1-esterase inhibitor becomes depleted are associated with a poor outcome after major surgery.* (Br. J. Anaesth. 1993; **71**: 858–863)

KEY WORDS

Complications: multiple organ dysfunction syndrome. Measurement techniques: gastric intramucosal pH.

Contact activation resulting in coagulation, fibrinolysis and release of vasoactive peptides is a critical component of the normal healing process that follows the trauma of major surgery [1]. However, excessive activation of host inflammatory system is believed to result in the development of multiple organ dysfunction syndrome (MODS) [2]. Contact activation refers to the activation of plasma factor XII (FXII) [3]. In addition to sub-endothelial collagen and smooth muscle, certain proteases and endotoxin may activate FXII. FXII sits at the hub of a web of enzyme cascades including intrinsic and extrinsic coagulation, fibrinolysis, kinin generation and complement activation. Prekallikrein (PKK) is a precursor for the formation of kallikrein (KK) which acts on kininogens to liberate bradykinin, a potent vasoactive agent. The resultant amplification in signal generation through these systems with clot formation and the release of vasoactive peptides would result in chaos if there were not a series of feedback loops via natural inhibitors of all the enzyme systems. The known inhibitors of the contact system are C1-esterase inhibitor (which in normal plasma accounts for 52% and 98% of the inhibitory capacity of KK and activated factor XII (FXIIa), respectively [4–6]), α-2 macroglobulin, antithrombin III and protein C inhibitor. α-1 Antitrypsin is the major plasma inhibitor of activated factor XI and neutrophil elastase released from activated neutrophils. Heparin co-factor II inhibits thrombin, cathepsin G and other chymotrypsin like enzymes, but not KK, activated factor X or FXIIa [7]. The measurement of various plasma components of the contact system such as FXII, PKK and C1-esterase inhibitor, in addition to plasminogen and antithrombin III, has been suggested as a diagnostic tool and predictor of outcome in adult respiratory distress syndrome (ARDS) and MODS [8–14]. There are preliminary results suggesting that the administration of clinical concentrates of inhibitors of the contact system may modify the outcome in established sepsis [15, 16]. Therefore, it would seem that the magnitude of contact activation, the level of naturally occurring inhibitors, or both, may be important determinants of outcome after major surgery.

Splanchnic hypoperfusion is common during major surgery and may lead rapidly to imbalance between pro-enzymes and inhibitors of the contact system [17, 18]. The gastric tonometer allows non-invasive assessment of gut mucosal perfusion, and

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thus splanchnic perfusion, by calculation of the gastric intramucosal pH (pHi) [19, 20]. A decreased pHi measured during major surgery is associated with a poor outcome [19, 21, 22]. Therefore, we have examined the incidence of gut mucosal ischaemia occurring during major surgery using the tonometer and related these findings to patient outcome and changes in components of the contact system.

PATIENTS AND METHODS

The study was approved by our local Ethics Committee and all patients gave written informed consent. Patients were studied if they were having elective major surgery of an anticipated duration of greater than 2 h which required routine arterial cannulation and central venous catheterization, and were at risk of developing gut mucosal hypoperfusion and post-operative organ failure according to published criteria [19, 21, 23, 24]. The following were exclusion criteria: age less than 18 yr, pregnancy, coagulopathies, perforated viscus, oesophageal or gastric pathology, oesophageal or gastric surgery, non-pulsatile cardiopulmonary by-pass, administration of aprotinin, regional anaesthesia. All patients were given an oral dose of ranitidine 150 mg the night before and on the morning of surgery to permit accurate assessment of gastric pHi [25]. All were anaesthetized as follows: premedication with papaveretum 15–20 mg and hyoscine 0.3–0.4 mg; alfentanil as a bolus of 25 $\mu g\ kg^{-1}$, followed by an infusion of 25 $\mu g\ kg^{-1}\ h^{-1}$. Anaesthesia was induced with a dose of thiopentone sufficient to obtund the eyelash reflex and the trachea was intubated after administration of atracurium 0.5 $mg\ kg^{-1}$. This was followed by an infusion of atracurium 0.5 $mg\ kg^{-1}\ h^{-1}$. The lungs were ventilated with 50 % nitrous oxide and isoflurane or enflurane in oxygen. Ventilation was adjusted to maintain Pa_{CO_2} at 4.5–5.5 kPa throughout. Depth of anaesthesia was gauged by clinical signs according to the anaesthetist's standard practice. For those patients undergoing cardiopulmonary bypass, the infusions of alfentanil and atracurium were continued but the nitrous oxide and volatile anaesthetic agent were stopped and patients were given a single bolus of lorazepam 2 mg i.v. Otherwise, no attempt was made to influence the anaesthetic or surgical management of the patients. Immediately after induction of anaesthesia a tonometer (Tonometrics Inc., Bethesda, MD) was inserted into the patient's stomach and its position confirmed by injection of air down the nasogastric tube whilst auscultating over the epigastrium. The tonometer was used to measure $P\text{CO}_2$ in the stomach after an equilibration period of 60 min and again at the end of surgery. pHi was calculated by substituting gastric $P\text{CO}_2$ and arterial bicarbonate determined by arterial blood-gas analysis (Radiometer 300 L, Copenhagen, Denmark) into a modified Henderson–Hasselbach equation as described and validated previously [19, 26]. pHi < 7.32 was taken as the lower limit of normality based on the results of previous studies [21, 22]. Theatre staff were blind to the results of all non-routine measurements. Immediately after induction of anaesthesia, at the time of placement of a multi-lumen central venous catheter, 10 ml of blood was aspirated from an internal jugular vein via a 14-gauge needle. A second sample was collected from a 16-gauge non-heparinized lumen of the central venous catheter 24 h after induction of anaesthesia, after removal of a 10-ml deadspace sample. Plasma was separated within 20 min of collection by centrifugation at 2000 *g* for 15 min at room temperature, divided into aliquots and stored immediately at −70 °C until required for analysis.

PCV, white blood cell (WBC) and platelet counts were measured by standard methods. FXII, plasminogen, PKK, antithrombin III, α-2 macroglobulin, α-1 antitrypsin and heparin co-factor II were measured by amidolytic substrate assays [27–31] using commercial reagents (Unicorn Diagnostics Ltd, London, U.K.), C1-esterase inhibitor was measured using a similar method (Immuno Ltd, Dunton Green, U.K.). FXII and PKK were assayed with highly specific substrates, using methods which were not affected by deficiencies of other contact factors. All amidolytic assays were standardized using reference plasma 100 % (Immuno Ltd, batch 1AOA), assuming a potency of 100 iu dl^{-1} for FXII, PKK, plasminogen, α-1 antitrypsin and heparin co-factor II. The standard was found to have an α-2 macroglobulin activity of 172 iu dl^{-1} when calibrated against pooled normal plasma. Neutrophil elastase:α-1 antitrypsin complexes were measured using an ELISA similar to that described by Galloway, Mackie and McVerry [32], with polyclonal antibodies to neutrophil elastase in the coating phase and peroxidase conjugated antibodies to α-1 antitrypsin (Serotec, Oxford) in the second phase.

Postoperative complications were recorded, a major complication being defined as one that resulted in an overall postoperative hospital stay of greater than 14 days or death [33]. Organ failure was determined according to the criteria proposed by Knaus and colleagues [34].

Data are shown as geometric mean and 2SD for the assay results and mean, (median) [range] for patient data. Differences between groups were analysed by the Mann–Whitney test and within groups by Wilcoxon's signed rank test. $P < 0.05$ was considered significant.

RESULTS

We studied 26 patients having elective major surgery. Type of surgery is shown in tables I and II. Of the 26 patients, 16 developed gut mucosal ischaemia (pHi < 7.32). Of this group, eight developed major

TABLE I. *Type of surgery. Patients grouped according to pHi at the end of surgery*

Type of surgery	pHi ⩾ 7.32	pHi < 7.32
Coronary artery by-pass graft	6	9
Heart valve replacement	3	3
Vascular surgery with aortic cross-clamp	1	4

TABLE II. *Patient characteristics of study population, duration of surgery, hospital stay, morbidity and mortality (number or mean (median) [range])*

	pHi < 7.32 ($n = 16$)	pHi $\geqslant 7.32$ ($n = 10$)
Sex (M:F)	12:4	7:3
Age (yr)	65 (67) [43–82]	64 (67) [40–75]
Weight (kg)	72 (75) [46–91]	73 (71) [48–99]
Height (cm)	168 (173) [128–183]	167 (173) [145–187]
Duration of op. (min)	231.7 (229) [130–310]	218.0 (195) [131–362]
Days in ITU	3.9 (1.0) [0–33]	1.1 (1.0) [1.0–2.0]
Days in hospital	16.7 (8.5) [2–97]	7.6 (7.0) [6–12]
Major complications	8	0
MODS	4	0
Deaths	3	0

TABLE III. *Components of the contact system measured by amidolytic substrate assays, comparing patients who developed gut mucosal ischaemia (pHi < 7.32) during major surgery to those who maintained gut mucosal perfusion (pHi $\geqslant 7.32$) (geometric mean (-2 SD/$+2$ SD)). NE = Neutrophil elastase; α-1AT = α-1 antitrypsin; FXII = factor XII; PKK = prekallikrein; ATIII = antithrombin III; HCII = heparin co-factor II; α-2M = α-2 macroglobulin; C1-INH = C1-esterase inhibitor. Significant differences*: *P < 0.05, **P < 0.01 *compared with baseline (within groups Wilcoxon signed rank)*; ††P < 0.01 *compared with baseline (between groups Mann–Whitney* U)

	Normal range	Baseline	24 h
pHi < 7.32 ($n = 16$)			
NE:α-1AT (μg litre^{-1})	30–172	134.9 (32.1/567.6)	372.4 (130.9/1088.9)**
FXII (iu dl^{-1})	70–140	73.0 (47.3/118.9)	52.6 (27.2/101.6)**
Plasminogen (iu dl^{-1})	70–140	79.0 (31.3/200.0)	51.5 (22.8./116.4)**
PKK (iu dl^{-1})	70–130	94.9 (184.1/48.9)	55.2 (26.1/117.0)**
ATIII (iu dl^{-1})	80–120	96.5 (46.0/202.8)	56.6 (14.9/215.3)**
HCII (iu dl^{-1})	65–148	80.8 (53.3/122.2)	49.5 (30.1/81.3)**
α-2M (iu dl^{-1})	70–150	104.4 (47.4/201.4)	60.7 (35.1/98.6)**
α-1AT (iu dl^{-1})	70–150	109.8 (70.0/172.6)	97.5 (48.2/197.2)
C1-INH (iu dl^{-1})	70–130	102.4 (52.5/199.5)	74.2 (32.8/167.5)††**
pHi $\geqslant 7.32$ ($n = 10$)			
NE:α-1AT (μg litre^{-1})	30–172	118.1 (52.5/265.5)	170.3 (65.3/443.6)
FXII (iu dl^{-1})	70–140	81.3 (40.2/164.4)	51.6 (27.6/96.6)**
Plasminogen (iu dl^{-1})	70–140	87.8 (71.3/107.9)	49.8 (20.9/118.3)**
PKK (iu dl^{-1})	70–130	104.8 (80.9/135.5)	54.2 (24.2/121.3)*
ATIII (iu dl^{-1})	80–120	97.3 (71.4/132.4)	68.3 (22.7/205.1)*
HCII (iu dl^{-1})	65–148	83.5 (55.3/126.5)	58.6 (30.9/111.2)*
α-2M (iu dl^{-1})	70–150	95.6 (57.3/152.1)	59.7 (28.6/110.6)**
α-1AT (iu dl^{-1})	70–150	106.8 (77.1/148.3)	112.2 (71.5/176.2)
C1-INH (iu dl^{-1})	70–130	87.4 (51.4/148.3)	87.1 (61.4/123.6)

complications (one cerebrovascular accident, one persistent dyspnoea, one ileus with persistent nausea and vomiting, one haematemesis requiring blood transfusion and four MODS). Of the four patients who developed MODS, three subsequently died. One patient required inotropic support at the end of surgery (isoprenaline and dopamine). This patient had an abnormal pHi and subsequently developed MODS and died. Ten patients maintained gut mucosal perfusion (pHi $\geqslant 7.32$); none of these developed major complications.

For both groups, there was a significant reduction in PCV and platelet count, but an increase in WBC. However, there were no differences in baseline values or magnitude of change between the two groups. For both groups there were significant reductions in concentrations of FXII, plasminogen, PKK, antithrombin III, α-2 macroglobulin and heparin co-factor II (table III). For both groups there was no significant reduction in α-1 antitrypsin concentration (table III). In the ischaemic group, there was a significant increase in neutrophil elastase concentration ($P < 0.005$) (fig. 1) and significant reduction in the concentration of C1-esterase inhibitor ($P < 0.005$) (table III, fig. 2). However, in the non-ischaemic group, neutrophil elastase concentration was not increased (fig. 1) nor C1-esterase inhibitor decreased (table III, fig. 2). There were no significant differences between groups for any of the baseline measurements. In the decreased pHi group, one patient had an abnormally great baseline concentration of neutrophil elastase (fig. 1) for which there was no obvious clinical reason. By 24 h it had decreased and the patient's postoperative course was uneventful. There was no difference between the groups in the number of patients with a decreased baseline concentration of C1-esterase inhibitor (two in each group). However, the smallest value (46 iu dl^{-1}) was recorded in a patient who developed MODS and died. Of the 16 patients who developed decreased pHi, 15 had increased concentrations of neutrophil elastase (> 170 μg litre^{-1}) at 24 h, compared with three in the normal pHi group. All three patients who developed MODS and subsequently died had concentrations of neutrophil elastase > 500 μg litre^{-1} by 24 h.

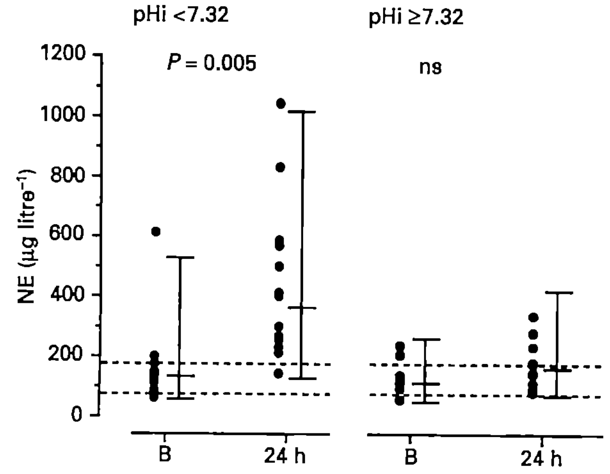

FIG. 1. Changes in plasma neutrophil elastase (NE) concentrations from baseline (B) to 24 h, for patients allocated to two groups according to the pHi at the end of surgery. Solid horizontal lines represent the geometric mean and 2 SD; broken lines represent normal range.

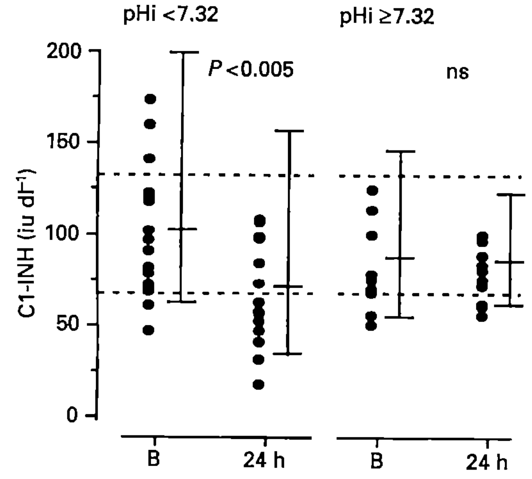

FIG. 2. Changes in plasma C1-esterase inhibitor (C1-INH) concentrations from baseline (B) to 24 h, for patients allocated to two groups according to the pHi at the end of surgery. Solid horizontal lines represent the geometric mean and 2 SD; broken lines represent normal range.

DISCUSSION

These data suggest that gut mucosal hypoperfusion, neutrophil degranulation and contact activation are associated with a poor outcome after major surgery if natural inhibitors of inflammatory pathways become depleted.

This confirms the results of previous studies which found that, irrespective of the type of surgery, the development of decreased perioperative pHi, suggesting splanchnic hypoperfusion, is a sensitive early predictor of postoperative morbidity and mortality [19, 21, 22]. These data also support the hypothesis that the degree of activation of inflammatory pathways is a major factor in the development of MODS [35]. The patients in the decreased pHi group had significantly greater concentrations of neutrophil elastase at 24 h, suggesting increased neutrophil degranulation and depletion of the protease inhibitor, C1-esterase inhibitor (by complexing with a wide variety of possible target proteases). These results are similar to those of Nuijens and colleagues [36], who found significantly greater concentrations of neutrophil elastase in patients with sepsis who died compared with those who survived. In the same study, neutrophil elastase concentration was found to vary in inverse relation to that of C1-esterase inhibitor. We did not find any difference between the decreased and normal pHi groups in the degree of coagulation or contact system activation, as judged by perioperative reductions in factor XII and PKK. Similarly, there was no difference in the degree of depletion of antithrombin III, α-2 macroglobulin, heparin co-factor II and α-1 antitrypsin, which are natural inhibitors of the coagulation and contact systems. It is a potential criticism of our data that the reduced concentrations of many of the components of the contact system may have been caused by dilution by administration of crystalloid and colloid solutions or extravasation through leaky endothelium. However, PCV correction of plasma concentrations of the various components was unable to support this hypothesis, as was the fact that the concentration of some plasma components, most notably C1-esterase inhibitor and neutrophil elastase, increased in many patients.

The known inhibitors of the contact system are C1-esterase inhibitor, α-2 macroglobulin, antithrombin III and protein C inhibitor [4–7], while α-1 antitrypsin is the major plasma inhibitor of neutrophil elastase [7]. The discrepancy between the two groups in the reduction in C1-esterase inhibitor, despite parallel decreases in the concentrations of PKK and FXII, suggests either that additional proteases (perhaps cellular, or from complement activation) are generated in the decreased pHi group, or that other plasma protease inhibitors have been compromised, leading to secondary depletion of C1-esterase inhibitor. The lack of difference between the two groups in the reduction in α-1 antitrypsin concentration, despite a significant difference in neutrophil elastase activity, may be caused by the enormous excess of plasma α-1 antitrypsin compared with released neutrophil elastase.

Inflammation is an essential component of the healing process [1]. From a wide variety of stimuli (trauma, burns, infection), the final common pathway results in vasodilatation, increased endothelial permeability, thrombosis and leucocyte emigration and activation [2, 8, 34]. Successful localization to the site of injury should result in resolution and healing. The systemic inflammatory response syndrome (SIRS) is a failure of localization. Multiple organ dysfunction syndrome (MODS) resulting from tissue damage in organs distant from the site of the original injury is the clinical manifestation of SIRS [2, 8, 34] and remains the major cause of mortality in the ITU [37]. Irrespective of the initiating stimulus (surgery, bacterial infection, pancreatitis) the morphology of postmortem specimens in both animal models and patients is remarkably constant. There is microvascular occlusion, endothelial destruction, interstitial oedema, leucostasis and thrombosis [38, 39]. Thus there would seem to be a dichotomy: inflammation is essential for successful recovery from major surgery, yet an excessive and uncontrolled inflammatory response may result in MODS. One hypothesis is that there is a level of stimulation that, when exceeded, leads to uncontrolled activation of inflammatory pathways [35]. There would appear to be a critical balance between activation and modulation. In this study, all patients had major surgery of similar magnitude, with no obvious difference as judged by type, duration and difficulty in those who had a poor outcome. Therefore, either host response was variable or additional activation of inflammatory pathways compounded the insult of surgery.

Tissue hypoperfusion is a common denominator in the pathogenesis of MODS [40–42]. It has been postulated that the integrity of the gut mucosal barrier is compromised by the ischaemia which is associated with hypovolaemia and subsequent compensatory splanchnic vasoconstriction [43]. This loss of integrity results in bacterial translocation, and the subsequent lysis of these bacteria, releasing cell wall products (endotoxin), is associated with stimulation of inflammatory pathways the main purpose of which is to prevent the invasion of micro-organisms [44].

It was decided that sampling at 24 h would be the most efficient single point for detecting changes in the plasma components measured. It seems most likely that the compounding insults of the trauma of surgery, plus gut mucosal ischaemia, plus the translocation of gut luminal contents could lead to excessive activation of inflammatory pathways as demonstrated by the increased concentrations of neutrophil elastase and depletion of C1-esterase inhibitor in those patients who developed gut mucosal hypoperfusion and had a poor outcome. However, it may be that the early depletion of natural inhibitors leads to an imbalance between coagulant and fibrinolytic pathways and results in microvascular thromboembolism manifest as gut mucosal ischaemia. We are currently carrying out a study to examine changes in gut mucosal perfusion and contact activation in the immediate perioperative period, to determine the temporal relationship of the changes observed.

When organ failure is likely or established, it may be possible to attempt to restore microvascular flow by a combination of therapies aimed at decreasing neutrophil adherence and degranulation, damping down the generalized inflammatory reaction and restoring the balance between coagulant and fibrinolytic pathways (e.g. C1-esterase inhibitor and antithrombin III). The administration of clinical concentrates of C1-esterase inhibitor and antithrombin III have been shown to modify outcome in animal models of septic shock [45–47]. There are preliminary results suggesting similar advantages in humans [16]. It would seem that greatest success might be anticipated with the early use of such therapies with the aim of preventing organ failure. Tonometry is a useful method of selecting a high risk group of elective surgical patients. Such a group of patients may benefit from the early use of inhibitor therapy, but rapid determination of inhibitor status would be required.

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LUNG MANAGEMENT DURING CARDIOPULMONARY BYPASS: IS CONTINUOUS POSITIVE AIRWAYS PRESSURE BENEFICIAL?

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SUMMARY

It is not clear if the use of continuous positive airway pressure (CPAP) during cardiopulmonary bypass (CPB) improves lung function after cardiac surgery. We have measured alveolar–arterial oxygen partial pressure difference $(PA_{O_2}-Pa_{O_2})$ *in 61 patients undergoing elective coronary artery bypass surgery. We studied three groups of patients: in group 1 the lungs were disconnected from the breathing system (no CPAP) during CPB; in group 2, 5 cm* H_2O *CPAP with air was applied to the lungs; in group 3, 5 cm* H_2O *of CPAP was applied with 100% oxygen.* $(PA_{O_2}-Pa_{O_2})$ *was measured before CPB and then at 30 min, 4 h and 8 h after CPB. Compared with group 1 (no CPAP),* $(PA_{O_2}-Pa_{O_2})$ *was significantly smaller in groups 2 and 3 at 30 min* ($P = 0.036$)*, but not at 4 h and 8 h after CPB* ($P = 0.32$, $P = 0.96$)*. The time to extubation* ($P = 0.42$) *and early extubation* ($P = 0.87$) *were not affected by the use of CPAP. The results of this study do not support the use of CPAP during CPB as a mechanism of improving lung function after cardiac surgery.* (Br. J. Anaesth. 1993; **71**: 864–868)

KEY WORDS

Lung: gas exchange. Surgery: cardiovascular.

Since the introduction of cardiopulmonary bypass (CPB) for cardiac surgery, there have been problems with respiratory dysfunction in the postoperative period. This has been termed "bypass lung" or "postperfusion lung syndrome" and is characterized by an increased alveolar–arterial oxygen partial pressure difference $(PA_{O_2}-Pa_{O_2})$ secondary to ventilation:perfusion ($\dot{V}:\dot{Q}$) mismatch, increased interstitial lung water and, possibly, alveolar capillary endothelial damage [1–3].

Improvements in anaesthesia, surgery and CPB technology have reduced the incidence and severity of bypass lung. However, the ideal management for the non-functioning lungs during CPB remains controversial and in studies on animal preparations and in humans various methods have been used to assess pulmonary function. These include pulmonary artery pressure, static and dynamic lung compliance, intrapulmonary shunting, arterial oxygen tension and extravascular lung water [1–13]. The clinical significance and relative importance of these indices remains in doubt, and are confounded by anaesthetic, surgical and perfusion techniques (e.g. ventilation settings, fluid therapy, use of a left atrial or ventricular vent, in-line filters, CPB prime solutions and type of oxygenator).

We have assessed the use of continuous positive airway pressure (CPAP) during CPB, attempting to control for many of these confounding variables. Postoperative respiratory function was assessed using $(PA_{O_2}-Pa_{O_2})$ and time to tracheal extubation after CPB.

PATIENTS AND METHODS

After obtaining Ethics Committee approval and informed consent, we studied patients undergoing elective coronary artery bypass grafting (CABG) in a prospective, randomized, double-blind design. Exclusion criteria included pulmonary disease requiring bronchodilator or steroid therapy and valvular heart disease requiring surgery. Patients who underwent ventilation for more than 72 h, or required reintubation of the trachea within 6 h of extubation, were excluded from further analyses. Patients requiring re-exploration in theatre were excluded also.

After preoxygenation, anaesthesia was induced and maintained with fentanyl 10–50 μg kg^{-1}, diazepam 2–10 mg, pancuronium 8–12 mg and 0–1% enflurane. Nitrous oxide was not used. All patients received an infusion of glyceryl trinitrate 20–60 μg min^{-1} from induction, with adjustment of the infusion rate at the discretion of the anaesthetist. Administration of inotropes and other vasoactive drugs was also left to the discretion of the anaesthetist and use was recorded.

CPB management was standardized using a combined crystalloid 1500 ml and colloid 500 ml prime, membrane oxygenator (Capiox E hollow fibre oxygenator: Terumo Corp., Tokyo, Japan; or Maxima hollow fibre oxygenator: Medtronic Cardiopulmonary Division, Anaheim, U.S.A.) and a 20-μm arterial line filter (Bentley AF-1025, Baxter Health Care, U.S.A.). No mannitol was added and blood cardioplegia was used. Hypothermia was regulated

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to a nasopharyngeal temperature of 25–27 °C, a mean arterial pressure of 50–70 mm Hg with non-pulsatile flow rates of 2.4 litre min^{-1} m^{-2} at 37 °C and 1.8 litre min^{-1} m^{-2} at 25 °C. Alpha-stat pH management was used and replacement fluids were added as blood (packed red cells), colloid or crystalloid as indicated. The left ventricle was vented in all cases.

Before CPB, intermittent positive pressure ventilation (IPPV) with oxygen in air (FI_{O_2} 0.5), tidal volume ($V\text{T}$) 10 ml kg^{-1} and ventilatory frequency to maintain the end-tidal carbon dioxide pressure ($F\text{E}'_{CO_2}$) at 4.0–4.7 kPa was used. (The HP M1176A monitor uses mm Hg as default unit for $F\text{E}'_{CO_2}$.)

After CPB, IPPV with FI_{O_2} 0.7, $V\text{T}$ 10 ml kg^{-1} and ventilatory frequency adjusted to maintain $F\text{E}'_{CO_2}$ at 3.3–4.3 kPa or arterial carbon dioxide tension (Pa_{CO_2}) 4.5–5.2 kPa. Positive end-expiratory pressure (PEEP) was not used, either before or after CPB.

During CPB the lungs were allowed to deflate, by disconnecting the breathing circuit (group 1 = no CPAP), were kept inflated by delivery of air 1.0 litre min^{-1} with CPAP (group 2 = air–CPAP) or were kept inflated by delivery of oxygen 1 litre min^{-1} with CPAP (group 3 = O_2–CPAP). CPAP was maintained via a circle system with airway pressure maintained at 5 cm H_2O by PEEP valve (Ambu International, Denmark). This was verified by a previously calibrated, in-circuit Bourdon gauge (Medishield, Commonwealth Industrial Gases Pty Ltd, Sydney, Australia).

Monitoring included 5-lead ECG, pulse oximetry, capnography, thermometry, invasive arterial pressure, right atrial pressure, pulmonary artery pressure and pulmonary capillary wedge pressure (PCWP). Cardiac output was measured via the pulmonary artery catheter using the thermodilution principle. These measurements were performed at room temperature, in triplicate, with each value accepted if within 10 % of each other. Derived haemodynamic variables (cardiac index (CI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI)) were calculated using Hewlett–Packard Component Monitoring system (HP M1176A, Hewlett–Packard GmBH, Hamburg, Germany).

Inspired oxygen concentration (FI_{O_2}) was measured using an Oxycheck oxygen analyser (Critikon Corp, Tampa, Florida, U.S.A.) in the operating theatre and with a Capnomac Ultima gas analyser (Datex Instrumentarium Corp., Helsinki, Finland) in the cardiothoracic intensive care unit. Arterial blood-gas tensions were measured using a Ciba–Corning 288 Blood Gas System (Ciba–Corning Diagnostics Corp., Medfield, MA, U.S.A.) 30 min after induction of anaesthesia and at 30 min, 4 h and 8 h after completion of CPB. PA_{O_2} was calculated using the alveolar gas equation, assuming an R value of 0.8 [14, 15]; ($PA_{CO_2} - Pa_{O_2}$) was then calculated.

Patient and operative characteristics were recorded, as were all fluids administered (as crystalloid, colloid and blood). Crystalloid volume included i.v. administration, cardioplegia, circulating pericardial cold solution and pressure-monitoring flush volume. Fluid balance was calculated at completion of CPB and at 8 h after CPB, by adding all administered fluids and subtracting blood loss, urine volume and nasogastric losses.

Bias control and statistics

The major confounding variables for our outcome assessment ($PA_{O_2} - Pa_{O_2}$) are those that may impair oxygen diffusion or result in $\dot{V}:\dot{Q}$ mismatch. These include pre-existing ($PA_{O_2} - Pa_{O_2}$) abnormalities, poor left ventricular function and excessive fluid administration during and after CPB. We therefore calculated ($PA_{O_2} - Pa_{O_2}$) for all patients before CPB and matched left ventricular function before operation. This was by block randomization and stratification according to preoperative left ventricular (LV) function. The operating surgeon assessed LV function when viewing the left ventriculogram before operation; each patient was classified as either "good ventricle" (normal or mild impairment) or "poor ventricle" (moderate or severe impairment).

Data sheets were coded, to blind the investigators and intensive care unit staff as to group identity (for collection of 4- and 8-h post-CPB results). Subsequent calculations and computer data entry were blinded also. Blinding could not be guaranteed during operation, although most cases were performed without an investigator present.

A preliminary estimate of sample size was calculated using Clinical Trials Design Program V1.0 (Biosoft, Cambridge, U.K.). From previous data [16], using a ($PA_{O_2} - Pa_{O_2}$) difference of 5.3 kPa and an SD of 5.3 kPa, we calculated 60 patients would achieve an alpha error of 0.05 and a beta error of 0.2 (power 80 %).

Parametric data were analysed using one-way analysis of variance. Multiple comparisons were corrected by the Student–Newman–Keuls procedure (SPSS/PC+ version 4.0 software). Data are presented as mean (SD) or median (range). All analyses were intention-to-treat (such that a patient randomized to the CPAP group but actually receiving no CPAP during CPB, would still be treated as belonging to that group). $P < 0.05$ was considered significant.

RESULTS

Sixty-one patients were entered into the trial: 17 patients in group 1 (no CPAP), 22 in group 2 (air–CPAP) and 22 in group 3 (O_2–CPAP). All three groups had similar patient characteristics (table I). One patient in group 3 underwent ventilation for more than 72 h after CPB (18 days); this patient had a prolonged postoperative course complicated by sepsis and renal failure. He eventually recovered. No patient required surgical re-exploration.

The mean age and body weight of the patients were 60.0 (8.8) yr and 78.9 (12) kg. The mean aortic cross-clamp time was 75 (28) min (range 32–149 min) and CPB time was 131 (44) min (range 45–228 min). At completion of CPB, patients had a net positive fluid balance of 3200 (1200) ml; at 8 h after CPB, net fluid balance was 3000 (1500) ml. The mean time to extubation (from the end of CPB) was 15.8 (12) h (median 12.9 h, range 5.3–432 h).

TABLE I. *Patient characteristics (mean (range or* SD*))*

	Group 1 ($n = 17$) No CPAP	Group 2 ($n = 22$) Air–CPAP	Group 3 ($n = 22$) O_2–CPAP
Sex (M/F)	12/5	16/6	14/8
Age (yr)	57.4 (40–75)	61.1 (43–75)	60.8 (47–79)
Weight (kg)	78.3 (12)	80.6 (14)	77.7 (11)
LV function			
Normal	9	3	7
Mild impairment	2	12	7
Mod. impairment	6	6	7
Severe impairment	0	1	1
Re-operation	0	3	1
No. of grafts	4.1 (0.90)	3.8 (0.97)	3.4 (1.2)
Cross-clamp time (min)	78.5 (33)	77.8 (26)	68.6 (27)
CPB time (min)	123 (43)	138 (33)	130 (55)

TABLE III. *Perioperative characteristics (mean* (SD))

	Group 1 ($n = 17$) No CPAP	Group 2 ($n = 22$) Air–CPAP	Group 3 ($n = 22$) O_2–CPAP
$(PA_{O_2}-Pa_{O_2})$ (kPa)			
Before CPB	18.3 (6.0)	18.0 (6.0)	21.1 (5.6)
Fluid balance (ml)			
After CPB	3400 (1100)	3200 (1200)	3080 (1300)
8 h after CPB	3150 (1700)	2950 (1400)	2950 (1600)
GTN ($\mu g\ min^{-1}$)			
Off CPB	32 (16)	26 (17)	21 (15)
In ICU	35 (23)	38 (21)	45 (26)
Adrenaline ($\mu g\ min^{-1}$)			
Off CPB	0.47 (1.4)	1.0 (2.3)	0.82 (2.0)
In ICU	0.76 (2.0)	0.91 (1.8)	1.2 (3.2)

The perioperative characteristics for the three groups were similar (tables II, III). In particular, the patients had similar haemodynamic function, $(PA_{O_2}-Pa_{O_2})$ before CPB and net fluid balance.

Before CPB, group 1 received 971 (260) ml of crystalloid and 29 (120) ml (median 0 ml, range 0–500 ml) of colloid, group 2 received 945 (470) ml of crystalloid and 145 (270) ml (median 0 ml, range 0–1000 ml) of colloid and group 3 received 1000 (410) ml of crystalloid and 68 (180) ml (median 0 ml, range 0–500 ml) of colloid; no patient received blood in the period before CPB. During CPB, group 1 received 3910 (1500) ml of crystalloid, 559 (120) ml of colloid and 35 (100) ml (median 0 ml, range 0–300 ml) of blood, group 2 received 3810 (1200) ml of crystalloid, 573 (180) ml of colloid and 27 (130) ml (median 0 ml, range 0–600 ml) of blood and group 3 received 3750 (1400) ml of crystalloid, 555 (120) ml of colloid and 27 (130) ml (median 0 ml, range 0–600 ml) of blood. In the 8-h period after CPB, group 1 received 546 (280) ml of crystalloid, 847 (790) ml of colloid and 53 (160) ml (median 0 ml, range 0–600 ml) of blood, group 2 received 535 ml of

TABLE II. *Haemodynamic changes (mean* (SD))

	Group 1 ($n = 17$) No CPAP	Group 2 ($n = 22$) Air–CPAP	Group 3 ($n = 22$) O_2–CPAP
Before induction			
Heart rate (beat min^{-1})	66.8 (14)	64.1 (12)	61.1 (11)
MAP (mm Hg)	91.1 (17)	82.6 (13)	89.5 (16)
PCWP (mm Hg)	10.0 (5.8)	9.2 (3.3)	8.7 (4.4)
Cardiac index (litre $min^{-1}\ m^{-2}$)	2.79 (0.95)	2.84 (1.1)	2.55 (0.50)
SVRI (dyn s $cm^{-5}\ m^{-2}$)	2650 (750)	2470 (750)	2690 (770)
PVRI (dyn s $cm^{-5}\ m^{-2}$)	231 (120)	202 (100)	255 (221)
After induction			
Heart rate (beat min^{-1})	64.5 (12)	68.7 (11)	67.1 (13)
MAP (mm Hg)	72.5 (12)	77.1 (9.7)	89.5 (16)
PCWP (mm Hg)	6.8 (3.5)	7.4 (3.9)	9.3 (5.0)
Cardiac index (litre $min^{-1}\ m^{-2}$)	2.16 (0.36)	2.19 (0.57)	2.25 (0.56)
SVRI (dyn s $cm^{-5}\ m^{-2}$)	2590 (420)	2790 (790)	2670 (740)
PVRI (dyn s $cm^{-5}\ m^{-2}$)	217 (64)	274 (140)	257 (103)
After CPB			
Heart rate (beat min^{-1})	86.5 (9.2)	85.5 (8.9)	87.6 (8.5)
MAP (mm Hg)	70.7 (7.3)	71.4 (8.9)	68.6 (13)
PCWP (mm Hg)	9.5 (3.6)	8.8 (4.0)	9.8 (3.6)
Cardiac index (litre $min^{-1}\ m^{-2}$)	2.84 (0.45)	2.95 (0.61)	2.87 (0.61)
SVRI (dyn s $cm^{-5}\ m^{-2}$)	1850 (400)	1810 (560)	1800 (500)
PVRI (dyn s $cm^{-5}\ m^{-2}$)	170 (91)	191 (79)	191 (93)
4 h after CPB			
Heart rate (beat min^{-1})	93.2 (11)	92.2 (14)	93.1 (14)
MAP (mm Hg)	78.2 (8.5)	76.0 (12)	76.4 (13)
PCWP (mm Hg)	8.4 (2.4)	9.5 (2.9)	10.1 (3.3)
Cardiac index (litre $min^{-1}\ m^{-2}$)	2.85 (0.81)	2.96 (0.85)	2.73 (0.56)
SVRI (dyn s $cm^{-5}\ m^{-2}$)	2190 (680)	2020 (580)	2190 (690)
PVRI (dyn s $cm^{-5}\ m^{-2}$)	265 (82)	264 (140)	232 (83)
8 h after CPB			
Heart rate (beat min^{-1})	89.5 (11)	98.1 (13)	92.6 (15)
MAP (mm Hg)	72.4 (12)	73.5 (7.7)	75.0 (9.1)
PCWP (mm Hg)	8.7 (2.8)	10.5 (2.3)	10.0 (3.4)
Cardiac index (litre $min^{-1}\ m^{-2}$)	2.68 (0.57)	2.82 (0.77)	2.92 (0.53)
SVRI (dyn s $cm^{-5}\ m^{-2}$)	2090 (470)	1980 (520)	1910 (430)
PVRI (dyn s $cm^{-5}\ m^{-2}$)	262 (64)	217 (79)	224 (63)

TABLE IV. *Respiratory outcome (mean (SD)). † Comparison between groups (ANOVA)*

	Group 1 (*n* = 17) No CPAP	Group 2 (*n* = 22) Air–CPAP	Group 3 (*n* = 22) O_2–CPAP	†*P*
$(PA_{O_2}-Pa_{O_2})$ (kPa)				
30 min CPB	43.3 (8.4)	35.5 (10.4)	36.8 (9.6)	0.036
4 h CPB	28.7 (11.5)	24.4 (11.3)	28.3 (9.6)	0.32
8 h CPB	26.4 (10.1)	25.7 (9.5)	26.9 (11.3)	0.96
Time CPB to extubation (h)	13.1 (4.5)	18.2 (16)	15.5 (11)	0.42

crystalloid, 495 (510) ml of colloid and 15 (70) ml (median 0 ml, range 0–330 ml) of blood and group 3 received 636 ml of crystalloid, 661 (680) ml of colloid and 82 (240) ml (median 0 ml, range 0–1000 ml) of blood.

There was a significant difference in $(PA_{O_2}-Pa_{O_2})$ 30 min after CPB, with air and oxygen CPAP resulting in better values compared with no CPAP ($F = 3.54$, $P = 0.036$) (table IV). However, this difference was no longer apparent at 4 h and 8 h after CPB ($F = 1.16$, $P = 0.32$; $F = 0.037$, $P = 0.96$, respectively). There was no difference between air and oxygen CPAP at any stage. There was no correlation between post-CPB $(PA_{O_2}-Pa_{O_2})$ and CI, cross-clamp time or CPB time.

The operating surgeon requested lung deflation in three patients in the CPAP groups because of difficulty with surgical access. This was temporary in two patients (30 min and 1 h), but was total for the third patient. There were several other occasions when the surgeon remarked on the difficulty with access.

Time to extubation (from the end of CPB) was not significantly different between the three groups ($F = 0.88$, $P = 0.42$) (table IV). If the patients were then classified according to early or late extubation of the trachea (before or after 13 h after CPB—approximately our median time to extubation), there was also no significant difference between the groups ($P = 0.87$).

DISCUSSION

We have found a significant reduction in $(PA_{O_2}-Pa_{O_2})$ in those patients who received 5 cm H_2O CPAP with air or oxygen during CPB, compared with those with no CPAP. This reduction was demonstrated only at 30 min after CPB and no benefit was seen in the CPAP groups at 4 h and 8 h after CPB. The mean time to extubation in all groups was not significantly different which suggests, in combination with the $(PA_{O_2}-Pa_{O_2})$ data, that no clinical benefit was achieved by applying CPAP to the lungs during CPB.

Difficulty with surgical access was found to be a significant problem with the use of 5 cm H_2O CPAP. Given the minor, transient benefit, we cannot recommend CPAP during CPB.

The pathophysiology of "bypass lung" is thought to involve damage to pulmonary capillary endothelium, followed by accumulation of interstitial fluid [1–3, 9, 11, 17]. The direct mechanism responsible for these changes is unclear; however, there is an association with microaggregates in the pulmonary capillaries. Damage may be initiated by activated leucocytes and the generation of oxygen free radicals, as demonstrated by a significant reduction in pulmonary injury after CPB using leucocyte filters [17–19] or plasmapheresis [20]. Careful filtration of all pump fluids (and probably the use of membrane, rather than bubble oxygenators) reduces the amount of microaggregates and resultant cellular oedema and damage.

Changes in $(PA_{O_2}-Pa_{O_2})$ are a clinically useful end-point to measure after CPB. Increases in both extravascular lung water (EVLW) and $\dot{V}:\dot{Q}$ mismatch increase $(PA_{O_2}-Pa_{O_2})$. Other factors are known to affect $(PA_{O_2}-Pa_{O_2})$ [1, 21]: cardiac output, oxygen extraction and shift in the haemoglobin–oxygen dissociation curve. However, our groups were matched for ventricular function, and haemodynamic indices after CPB were equivalent. There was no correlation with CI. We also standardized perfusion techniques using membrane oxygenators, arterial filters and standard pump primes while scrupulous recording of fluid balance and stratification by LV function enabled objective comparison of groups.

Previous workers have found increased pulmonary vascular resistance after CPB [1]. In our study, PVRI was smaller 30 min after CPB and was equal between groups. This may be because of advances in perfusion techniques (e.g. use of in-line filters minimizing microaggregate collection in the pulmonary circulation), and the routine use of glyceryl trinitrate.

Boldt and colleagues [2] investigated lung management during CPB by measuring EVLW, Pa_{O_2} and intrapulmonary shunting. $(PA_{O_2}-Pa_{O_2})$ was not measured directly. It was found that all patients increased EVLW after CPB, this being most pronounced in those groups receiving 15 cm H_2O CPAP during CPB. Lung water had returned to normal 5 h after post-CPB in all patients except those with no CPAP or 15 cm H_2O CPAP. Shunt and decreased Pa_{O_2} were also greatest in these groups. The authors concluded that pulmonary function can be maximized using CPAP of 5 cm H_2O (air) during CPB, but interpretation of this study is difficult. Their patients underwent ventilation before and after CPB with 100% oxygen and 5 cm H_2O PEEP; bubble oxygenators and crystalloid CPB prime were also used. The clinical relevance of EVLW remains obscure, as does the contribution of large inspired oxygen concentration and PEEP on this outcome measure [22–24].

Other studies have considered the effect of mechanical ventilation (IPPV) of the lungs during CPB [3, 4, 12]. These studies concluded that IPPV had deleterious effects on intrapulmonary shunting and lung compliance in the period after CPB and that it had no effect on systemic or pulmonary haemodynamic changes. Stanley, Liu and Gentry [4] also showed no benefit in "static inflation of the lungs" (4 and 8 cm H_2O CPAP) during CPB compared with a group with collapsed lungs.

Hewson and Shaw [9] have shown that there is a substantial shift of fluid from the interstitium into the cells of the lung after 2 h of CPB in rabbits. They also showed that, if the lungs are allowed to collapse for that period, they suffer a significant hypoxic energy deficit which can be prevented by applying "static pulmonary expansion with an oxygen rich mixture during CPB" (i.e. 5 cm H_2O CPAP). It is possible that those patients who had a reduced $(P\mathrm{A}_{O_2} - P\mathrm{a}_{O_2})$ 30 min after CPB in groups 2 and 3 in our study were demonstrating this effect. However, the advantage conferred on the CPAP groups was only short lived, implying that the energy deficit was reversible and its significance reduced by improving cardiac performance and $\dot{V}:\dot{Q}$ changes in the period after CPB.

Conflicting results from previous studies make it difficult to determine the ideal lung management during CPB. Many factors have been shown to affect lung function, but often the control of these has been poor. Our study has attempted to standardize confounding factors, and used clinically relevant outcome measures: $(P\mathrm{A}_{O_2} - P\mathrm{a}_{O_2})$ and time to extubation. Our results do not support the use of CPAP during CPB.

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COMPARISON OF THE HAEMODYNAMIC EFFECTS OF ENOXIMONE AND PIROXIMONE IN PATIENTS AFTER CARDIAC SURGERY

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SUMMARY

We have compared the haemodynamic effects of the imidazole derivative phosphodiesterase inhibitors enoximone and piroximone in patients with low cardiac output after cardiac surgery. Ten patients (group E) received enoximone and 10 patients (group P) received piroximone, both at a loading dose of 0.5 mg kg^{-1} followed by an infusion of 5 µg kg^{-1} min^{-1}. In both groups the main changes with time were increases in cardiac index (maximum 24.5% in group E, 25.8% in group P) and decreases in systemic vascular resistance (maximum 26.8% in group E and 24.8% in group P). There were moderate increases in heart rate (maximum 11.3% in group E and 13% in group P) but a greater percentage decrease in mean arterial pressure in group E (maximum 11.9% vs 7.9%) with time. One patient in group E developed hypertension during the loading dose. Two patients in group E and two in group P developed hypotension during the loading dose. One patient in group E developed ventricular extrasystoles which may have been related to the drug being studied. (Br. J. Anaesth. 1993; **71**: 869–872)

KEY WORDS

Phosphodiesterase inhibitors: enoximone, piroximone. Surgery: cardiac.

Enoximone and piroximone are imidazole derivatives with inotropic and vasodilator activity. They promote these effects by specific inhibition of a cyclic AMP (cAMP) phosphodiesterase (PDE III) in cardiac myocytes and vascular smooth muscle. This results in an increase in sarcoplasmic cAMP and cAMP-dependent phosphorylation of the proteins which control cellular calcium flux. This mechanism is independent of beta adrenergic receptors and so offers an alternative to catecholamine therapy in patients with endogenous or exogenous beta receptor tolerance [1] or beta receptor block [2].

The beneficial haemodynamic effects of enoximone and piroximone have been validated in patients with chronic heart failure. Recently there has been increased interest in the haemodynamic effects of PDE inhibitors in patients with decreased cardiac output after heart surgery—patients who require both inotropic and vasodilator therapy. The primary aim of this study was to compare the haemodynamic effects of i.v. enoximone and piroximone in patients with decreased cardiac output after cardiac surgery.

PATIENTS AND METHODS

After obtaining local Ethics Committee approval and written informed consent, we studied patients aged 18 yr or more with a stable decreased cardiac output state (defined as baseline cardiac index (CI) of less than 2.5 litre min^{-1} m^{-2} with a minimum pulmonary capillary wedge pressure (PCWP) of 8 mm Hg) after cardiac surgery. The baseline CI was the mean of two measurements obtained at least 10 min apart and reproducibility was confirmed if the measurements were within 15%. Patients were excluded if they had evidence of uncontrolled arrhythmias, inotropic therapy within 1 h of study or long acting vasodilator therapy within 12 h of the baseline measurements, PDE inhibitor therapy within 48 h of surgery and any preoperative evidence of hepatic or renal impairment. Patients were not entered or withdrawn

TABLE I. *Patient data (number or mean (range or SD))*

	Enoximone	Piroximone
No. of patients	10	10
Sex (M/F)	6/5	7/3
Age (yr)	58.7 (51–68)	61.2 (49–78)
Weight (kg)	77.0 (17.1)	83.6 (10.9)
Surface area (m^{-2})	1.83 (0.21)	1.93 (0.13)
Operation		
Coronary artery surgery (CAS)	6	9
Valve surgery (VS)	3	1
CAS+VS	1	0
Cardiopulmonary bypass time (min)	95.6 (32)	80.5 (21)
Myocardial ischaemia time (min)	56.8 (25)	44.6 (10)

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TABLE II. *Baseline haemodynamic state (mean (SD))*

	Enoximone	Piroximone	*P*
MAP (mm Hg)	82.1 (15)	71.5 (11.8)	0.05
PCWP (mm Hg)	10.3 (2.7)	10.1 (1.3)	ns
PAP (mm Hg)	18.8 (3.5)	17.5 (3.8)	ns
CI (litre min^{-1} m^{-2})	1.93 (0.3)	2.08 (0.3)	ns
HR (beat min^{-1})	82 (13.8)	73 (12.1)	ns
SV (ml)	44.2 (9.5)	56.1 (7.3)	0.01
RVEF	0.36 (0.07)	0.40 (0.09)	ns
RVESV (ml)	79.3 (19.2)	87.1 (27.1)	ns
RVEDV (ml)	123 (20.5)	144 (25.7)	0.05
SVR (dyn s cm^{-5})	1734 (450)	1252 (119)	0.01
PVR (dyn s cm^{-5})	216 (56)	157 (86)	0.05
LVSWI (g m m^{-2})	23.7 (7.2)	24.1 (5.6)	ns

from the study if they required additional short acting inotropic or vasodilator therapy.

Twenty-one patients were allocated randomly to receive either enoximone (E) (11 patients) or piroximone (P) (10 patients) and drug administration was open. One patient in group E was withdrawn from the study and the statistical analysis was made on the remainder (table I). Anaesthesia was not standardized, but was based on an opioid premedication and a fentanyl and sedation technique without volatile agents. The lungs were ventilated by intermittent positive pressure throughout the study and sedation was by intermittent opioids (i.v. papaveretum or morphine 2.5–5 mg) and a continuous infusion of propofol 1–2 mg kg^{-1} h^{-1} as required. Fluid therapy comprised continuous infusion of 5% glucose 0.5 ml kg^{-1} h^{-1} with blood, plasma or Haemaccel as indicated clinically from the PCWP and arterial pressure measurements. Pressures were measured via a right ventricular function thermodilution pulmonary artery (Baxter–Edwards) and radial artery cannula, using the mid axilla as the zero reference point. ECG was monitored continuously. Cardiac output and right ventricular function were measured in triplicate using the Baxter REF-1 cardiac output computer.

The study period was from the baseline measurement until 3 h after the start of infusing the study drug. Patients in group E received a loading dose of enoximone 0.5 mg kg^{-1} over 20 min followed by an infusion of 5 μg kg^{-1} h^{-1}. Patients in group P received a loading dose of piroximone 0.5 mg kg^{-1} over 20 min followed by an infusion of 5 μg kg^{-1} h^{-1}. Mean arterial pressure (MAP), PCWP, mean pulmonary artery pressure (PAP), right atrial pressure, cardiac output (CO), heart rate (HR), stroke volume (SV), right ventricular ejection fraction (RVEF), right ventricular end-systolic volume (RVESV) and right ventricular end-diastolic volume (RVEDV) were recorded at baseline. These were repeated at 15, 30, 45, 60, 90, 120 and 180 min after the start of the

TABLE III. *Cardiovascular variables: percentage change from baseline (mean (SD)). E = Enoximone; P = piroximone.* **P < 0.05 compared with baseline*

	Time (min)				
	15	60	120	180	MANOVA
MAP (mm Hg)					
E	−9.1 (14)*	−11.9 (15)*	−10.0 (13)*	−11.2 (12)*	0.01
P	−7.9 (14)*	2.2 (9)	−0.7 (9)	−2.7 (10)	0.05
PCWP (mm Hg)					
E	−13.9 (37)	−3.2 (41)	−12.6 (37)	−17.7 (23)	ns
P	−11.7 (17)	−16.4 (25)	−13.6 (24)	−9.2 (21)	ns
PAP (mm Hg)					
E	−4.3 (20)	−1.4 (23)	−1.6 (22)	2.9 (23)	ns
P	0.4 (11)	6.8 (20)	9.0 (15)	8.4 (15)	ns
CI (litre min^{-1} m^{-2})					
E	14.2 (13)	23.8 (18)*	20.1 (14)*	24.5 (19)*	0.001
P	25.8 (16)*	15.3 (19)*	18.9 (17)*	19.8 (14)*	0.001
HR (beat min^{-1})					
E	5.6 (11)	11.3 (11)*	9.1 (10)*	8.8 (11)*	0.01
P	13.0 (11)*	8.4 (11)*	8.2 (14)	11.1 (13)*	0.001
SV (ml)					
E	8.2 (11)	13.2 (25)	10.9 (17)	16.4 (27)	ns
P	11.7 (11)*	6.5 (14)	10.0 (15)	9.3 (15)	0.05
RVEF					
E	−0.7 (22)	8.4 (25)	10.0 (20)	15.7 (25)	ns
P	9.8 (12)	7.7 (19)	14.9 (22)	7.5 (17)	ns
RVESV (ml)					
E	18.1 (47)	7.7 (49)	0.7 (41)	−1.5 (43)	ns
P	−3.3 (14)	−2.2 (19)	−8.5 (20)	−5.3 (21)	ns
RVEDV (ml)					
E	14.9 (31)	10.2 (35)	5.0 (27)	1.4 (22)	ns
P	2.0 (9)	1.0 (15)	−2.3 (11)	−0.6 (14)	ns
SVR (dyn s cm^{-5})					
E	−18.4 (20)*	−25.9 (19)*	−24.0 (19)*	−26.8 (19)*	0.001
P	−24.8 (14)*	−7.4 (13)	−13.4 (14)*	−17.1 (17)*	0.001
PVR (dyn s cm^{-5})					
E	−7.9 (31)	−14.2 (30)	−11.2 (29)	−5.8 (28)	ns
P	−3.8 (20)	32.4 (54)	30.3 (49)	25.3 (52)	ns
LVSWI (g m m^{-2})					
E	2.0 (13)	−1.5 (25)	−2.4 (16)	3.7 (29)	ns
P	5.2 (16)	13.5 (20)	12.9 (19)	7.7 (21)	ns

study drug. Systemic (SVR) and pulmonary (PVR) vascular resistances and left ventricular stroke work index (LVSWI) were derived using standard formulae.

Statistical methods

Patient characteristics were assessed by *t* test and Fisher's exact probability test as appropriate. The changes with time were assessed by multiple analysis of variance (MANOVA) for repeated measures using the SPSS statistical package. As appropriate for small groups, significance was also tested using Wilcoxon signed rank. $P < 0.05$ was considered statistically significant.

RESULTS

There were no significant differences between the groups in sex, weight, surface area, type of surgery or bypass times (table I).

The comparative baseline haemodynamic measurements of the two groups are presented in table II. MAP, SVR and PVR were greater and SV and RVEDV less in group E compared with group P. The only difference between the groups with time was a significantly greater percentage decrease in MAP in group E from 45 to 120 min inclusive.

Table III presents the percentage changes from baseline in each group. Although the analysis included the measurements at all times, only those at 15, 60, 120 and 180 min are tabulated. In both groups, the main changes were significant increases in CI, and decreases in SVR. There were moderate increases in HR and decreases in MAP, and an increase in SV in group P. The remainder of the measured and derived variables were unchanged.

Hypertension which developed during the loading dose was reported in one patient in group E. SAP increased from 112 mm Hg to 139 mm Hg and was treated with specific hypotensive therapy outside the study design. This patient was withdrawn from the study.

Hypotension which developed during the loading dose occurred in four patients, who were not withdrawn from the study. In two patients from group E, SAP decreased by 30–50 % and was treated by rapid infusions of fluid. In one patient from group P, SAP decreased by 30 % and was treated by i.v. fluids and calcium chloride 5 mmol. One other patient in group P developed mild hypotension which required no specific treatment. No patient was hypotensive during the subsequent infusion.

Only one patient, who was in group E, developed a rhythm disorder which might have been related to the study drug. This was unifocal ventricular ectopic activity which was not serious and the infusion was continued unchanged.

DISCUSSION

Previous studies have investigated enoximone given before [2], during [3–7] and after [8–10] cardiopulmonary bypass. At present there is limited experience of piroximone in cardiac surgical patients [11–13].

The choice of drug doses used in this study was based on previous studies in patients undergoing cardiac surgery. Beneficial haemodynamic effects of enoximone and piroximone have been demonstrated after recommended loading doses of 0.5 mg kg^{-1} [7, 9, 12–14] and maintenance infusions of enoximone 5 μg kg^{-1} min^{-1} [8] or piroximone 3–6 μg kg^{-1} h^{-1} [13]. It was important to have a stable baseline for comparisons because the numbers in each group were small. By conducting this study in the intensive care unit on patients with stable decreased cardiac output and using the mean of two baseline measurements with good reproducibility, we established that any significant changes in haemodynamics were likely to be caused by the study drug.

Baseline haemodynamic state showed that group E had a greater degree of vasoconstriction (SVR and PVR) which led to the baseline differences in MAP and SV. The presence of baseline differences in small groups is not surprising, but it does validate the use of percentage changes from baseline to detect differences between groups. The greater decrease in MAP in group E may represent true differences in actions of the drugs. However, it may also be caused by greater baseline vasoconstriction in group E or non-equipotent dose regimens. We found the patterns of haemodynamic response in the two groups interesting (fig. 1). In group E, the haemodynamic changes were early and sustained,

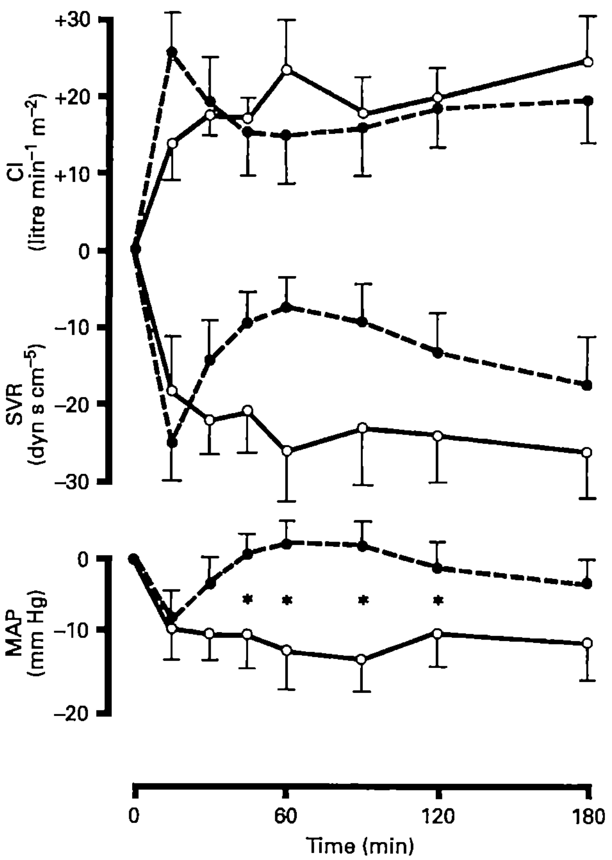

FIG. 1. Mean (SEM) percentage changes in cardiac index (CI), systemic vascular resistance (SVR) and mean arterial pressure (MAP) in the enoximone (○) and piroximone (●) groups. * Significant difference between groups ($P < 0.05$).

and this is predictable from the pharmacokinetic profiling of Gonzalez and co-workers using similar dosing schedules [8]. In group P, for MAP, CI and SVR there was maximal change at 15 min with a return towards baseline values at 60 min and progressive changes thereafter. The difference may be related to the serum concentrations of the drugs. Theoretically, the larger volume of distribution of piroximone (2.5 litre kg^{-1}) [15] compared with enoximone (1.6 litre kg^{-1}) [16] may result in a greater decrease after the loading dose, perhaps to less than therapeutic values, until a greater concentration is restored by the infusion. Further investigation is required to determine ideal loading and infusion doses of piroximone, possibly using step-down infusion regimens.

The haemodynamic changes observed in this study are in broad agreement with those found by others. There was a significant increase in CI, closely associated with a decrease in SVR. As changes in loading affect myocardial contractility, it was impossible to separate the contribution of inotropic and vasodilator effects. However, after cardiac surgery both properties are desirable and we found both drugs appropriate and beneficial. In contrast with others, we could not comment on the effect of the drug on PCWP as our practice was to compensate for large decreases by infusing fluids. However, some patients had profound decreases in PCWP as reflected in the large SD and these individuals may have benefited from greater fluid therapy. As PDE inhibitors have pulmonary vasodilating properties and are beneficial in patients with mitral valve disease [13], we were interested to detect effects on right ventricular function using the RVEF catheter. Our patient population was not entirely appropriate. In general, these patients did not have pulmonary hypertension or compromised right heart function, therefore it was not surprising that we did not detect significant changes in right ventricular function. We did note a consistent, non-significant increase in mean RVEF in both groups and so feel that the effect of these drugs in right heart failure requires closer investigation.

Transient severe hypotension was a complication during the loading dose in three patients who had PCWP in the range 9–11 mm Hg. The hypotension was corrected rapidly and not associated with ECG evidence of ischaemia. It could be argued that our initial filling pressures should have been greater. However, we are cautious with fluid preloading in patients with decreased cardiac output after cardiac surgery. It may be that giving the loading dose over 20 min was too rapid. With careful monitoring, slower loading dose infusions and an awareness of the potent vasodilator effects of these drugs, hypotension should not present a serious clinical problem.

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ISOFLURANE INHIBITS INSULIN SECRETION FROM ISOLATED RAT PANCREATIC ISLETS OF LANGERHANS†

J. P. DESBOROUGH, P. M. JONES, S. J. PERSAUD, M. J. LANDON
AND S. L. HOWELL

SUMMARY

We have investigated the effects of isoflurane on insulin secretion in vitro *from rat isolated islets of Langerhans and found a significant, dose-related and reversible inhibition of insulin secretion. Isoflurane 2% decreased insulin secretion stimulated by glucose 20 mmol litre*$^{-1}$ *to basal, non-stimulated values. In other studies to identify the stage in the stimulus secretion pathway for insulin at which the anaesthetic may exert an inhibitory action, we have stimulated insulin release using glyceraldehyde and a phorbol ester. Insulin secretion induced by these secretagogues was also blocked by isoflurane. This suggests that the inhibitory effect of the anaesthetic agent may be at a site distal to stimulation of insulin secretion by glyceraldehyde and phorbol esters.* (Br. J. Anaesth. 1993; **71**: 873–876)

KEY WORDS
Anaesthetics, volatile: isoflurane. Metabolism: insulin secretion.

Volatile anaesthetic agents used during maintenance of anaesthesia may contribute to the hyperglycaemia associated with surgery by inhibition of insulin release. Halothane and enflurane have been shown to inhibit glucose-stimulated insulin secretion directly from pieces of rat pancreas and from rat isolated pancreatic islets of Langerhans [1,2]. The mechanisms by which these anaesthetics inhibit the stimulus–secretion pathway in insulin-secreting pancreatic islet β cells remain to be elucidated.

Glucose is the major physiological regulator of insulin secretion. After its transport into the β cell, its metabolism triggers the mechanism for insulin release via generation of intracellular second messengers and activation of protein kinases, leading to exocytosis of insulin [3]. A simplified view of the pathway of stimulus–secretion coupling for insulin release from a pancreatic β cell is shown in figure 1. Experimentally, insulin secretion may be stimulated in several ways. Glyceraldehyde is an intermediate in the glycolytic pathway and may be used to stimulate insulin secretion distal to the transport of glucose into the cell and the initiation of glucose metabolism. Diacylglycerol, produced during the turnover of membrane phospholipids, activates protein kinase C and is a potent insulin secretagogue [4]. Tumour-promoting phorbol esters, which mimic diacylglycerol, may also be used *in vitro* to stimulate release of insulin.

We have examined the effects of isoflurane on glucose-induced insulin secretion from rat isolated pancreatic islets of Langerhans *in vitro*, in static incubations and in a perifusion system which allows an assessment of dynamic changes in insulin secretion. We have also investigated the possible site of action of isoflurane using glyceraldehyde and a phorbol ester, phorbol myristate acetate (PMA), to stimulate insulin secretion.

METHODS

Wistar rats were killed by cervical dislocation before excision of the pancreas. Islets of Langerhans were isolated by collagenase digestion [5]. In this technique, the pancreatic duct is cannulated and 5 ml of collagenase solution 1 mg ml^{-1} injected, which

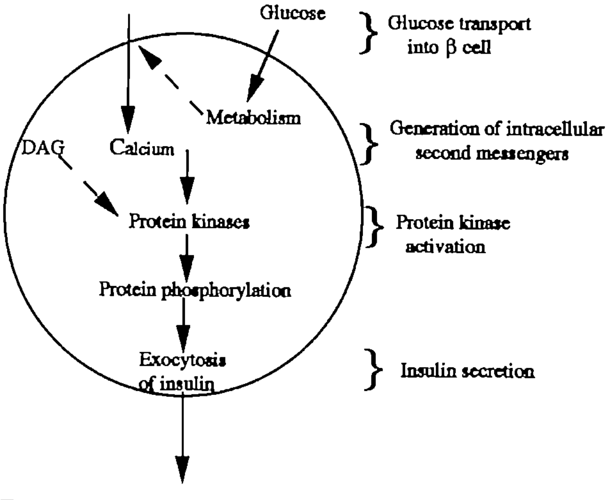

FIG. 1. Diagrammatic representation of stimulus secretion pathway of insulin secretion. DAG = Diacylglycerol.

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digests the exocrine tissue, thus allowing the islets of Langerhans to be picked from the digest using a finely drawn pipette under a dissecting microscope. The islets were pre-incubated for 30–60 min at 37 °C in a bicarbonate-buffered physiological salt solution (pH 7.4) containing glucose 2 mmol litre^{-1}, calcium chloride 2 mmol litre^{-1} and bovine serum albumin 0.5 mg ml^{-1}.

For static incubations, groups of three islets were placed in microcentrifuge tubes containing 100 µl of buffer as above. An additional 500 µl of buffer (Medium 199, Earles salts) containing the test substances of interest was then added to the tubes which were sealed and the preparation incubated in a water bath at 37 °C for 30 min. The islets were pelleted by centrifugation (9000 *g*, 15 s) and a supernatant sample of incubation buffer was taken and stored at −20 °C until required for subsequent measurement of insulin content by radioimmunoassay [6].

Basal insulin secretion was measured in groups of islets incubated in buffers containing glucose 5 mmol litre^{-1}. Insulin secretion was stimulated using glucose 20 mmol litre^{-1}, glyceraldehyde 10 mmol litre^{-1} or PMA 250 and 500 nmol litre^{-1}. To assess the effects of isoflurane on insulin secretion, incubation media were equilibrated by bubbling with a stream of 100% oxygen 1 litre min^{-1} (for 5 min at 20 °C) containing vaporized isoflurane (Ohmeda Mark 3 vaporizer). Control buffers were bubbled with oxygen alone. The required volume of buffer was then added rapidly to the microcentrifuge tubes containing the islets and the preparation incubated as above.

The partial pressure of isoflurane in the gas space above the buffer in the microcentrifuge tubes was measured by the headspace technique using gas chromatography [7]. The Pye 104 gas chromatograph (GC) used flame ionization detection and a pen recorder produced peaks corresponding to detection of isoflurane. Samples of buffer from duplicate microcentrifuge tubes were taken at intervals throughout the 30-min incubation period during static incubations using a vaporizer setting of 1% or 2% isoflurane. The samples of buffer were injected into glass vials sealed with Teflon–silicone liners. The gas headspace in these vials was allowed to equilibrate for 45 min by gentle rotation (20 r.p.m.) at 37 °C in a thermostatically controlled cabinet. A portion of the headspace was then flushed onto the GC column. The buffer sample and headspace were allowed to re-equilibrate and a series of three successive measurements made in duplicate from each buffer sample. For each series, the peak heights produced by the pen recorder were plotted on a logarithmic Y-axis against the equilibration number. The intercept on the Y-axis represented the partial pressure in the gas phase in the original sample. This was calculated using peak heights produced by calibration of the GC with isoflurane of a known partial pressure.

After isolation and preincubation of islets as described above, groups of 50 islets were placed in filter chambers containing nylon mesh filters and perfused simultaneously with buffer (Medium 199, Earles salts) containing the test substances of interest at a rate of 1 ml min^{-1} in a 37 °C environment. In this way, groups of islets were perifused with a sequence of buffers. The effluent perifusate emerging from the filter chambers was collected at 2-min intervals for measurement of insulin content. After initial perifusion for 10 min with glucose 5 mmol litre^{-1}, a stimulatory concentration of glucose (20 mmol litre^{-1}) was introduced. Subsequently, the effects of isoflurane were examined either by perifusing groups of islets with glucose 20 mmol litre^{-1} into which isoflurane 2% was bubbled (experimental group, $n = 6$), or by continuing to perifuse with glucose 20 mmol litre^{-1} alone (control group, $n = 4$).

Insulin secretion was measured by radioimmunoassay [6] using purified rat insulin as standard, guineapig anti-insulin serum and ^{125}I-labelled bovine insulin. The intra- and inter-assay coefficients of variation for this assay were 5.2% and 14%, respectively. Results are described as mean (SEM) insulin secretion (ng/islet 30 min^{-1}). For static incubations, differences between groups were analysed by Student's unpaired *t* test. In the perifusion experiment, differences between groups and within each group with time were assessed by analysis of variance. $P < 0.05$ was considered significant.

RESULTS

Effects on basal and glucose-induced insulin secretion in static incubation

Isoflurane had no effect on basal insulin release. In the presence of glucose 5 mmol litre^{-1}, insulin secretion was 1.78 (0.39) ng/islet 30 min^{-1}. With the addition of isoflurane 1% and 2%, insulin secretion in the presence of glucose 5 mmol litre^{-1} was not changed significantly (2.03 (0.31) and 1.97 (0.41) ng/islet 30 min^{-1}, respectively; $n = 9$ for all groups).

In another experiment (table I), insulin secretion was increased significantly in the presence of glucose 20 mmol litre^{-1}, from 1.35 (0.60) ($n = 7$) to 3.52 (0.62) ($n = 8$) ng/islet 30 min^{-1} ($P < 0.01$). This glucose-induced secretion was inhibited in a dose-dependent manner in the presence of isoflurane. With a vaporizer setting of 1% isoflurane, glucose-induced insulin secretion decreased to 1.70 (0.39) ($n = 9$) ng/list 30 min^{-1} ($P < 0.05$); with a setting of 2% isoflurane, secretion was 0.97 (0.20) ($n = 8$) ng/islet 30 min^{-1} ($P < 0.01$). Although this latter value was smaller than that with glucose 5 mmol litre^{-1} alone, the difference was not statistically significant. As the inhibition of glucose-induced insulin secretion in the presence of isoflurane was maximal with a vaporizer setting of 2% isoflurane, this setting was used for subsequent studies.

Perifusion (fig. 2)

The results of the perifusion experiment showed that, after a change in concentration of glucose in the perifusion medium from 5 mmol litre^{-1} to a stimulatory concentration of 20 mmol litre^{-1}, there was an immediate increase in insulin release from both control and experimental groups of islets. In

TABLE I. *Insulin secretion (mean* (SEM) *[95% confidence limits]) during static incubation.* †$P < 0.05$ *compared with glucose 5 mmol litre*$^{-1}$; *$P < 0.05$, **$P < 0.01$ *compared with glucose 20 mmol litre*$^{-1}$ *alone*

Glucose (mmol litre^{-1})	Isoflurane (%) (vaporizer setting)	*n*	Insulin secretion (ng/islet 30 min^{-1})
5	—	7	1.35 (0.60) [0.17–2.53]
20	—	8	3.52 (0.62) [2.30–4.74]†
20	0.5	8	2.17 (0.59) [1.01–3.33]
20	1.0	9	1.70 (0.39) [0.94–2.46]*
20	2.0	8	0.97 (0.20) [0.58–1.36]**

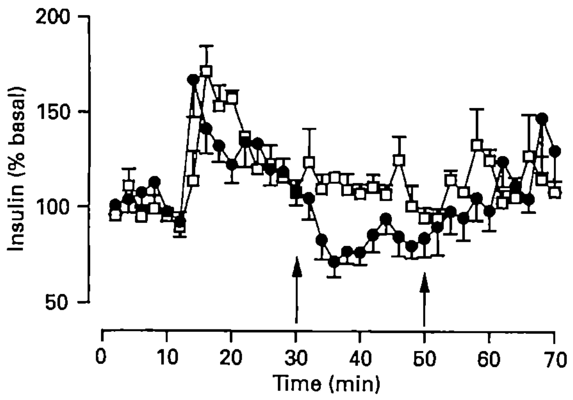

FIG. 2. Change in insulin secretion with time. Groups of 50 islets were perifused for 10 min with medium containing glucose 5 mmol litre^{-1}, after which the medium contained glucose 20 mmol litre^{-1}. Between 30 and 50 min (arrows), islets received either glucose and isoflurane (●; $n = 6$ experimental groups, mean (SEM)) or continued to receive glucose alone (□; $n = 4$ control groups, mean (SEM)). Significant difference between groups from 36 to 46 min ($P < 0.05$).

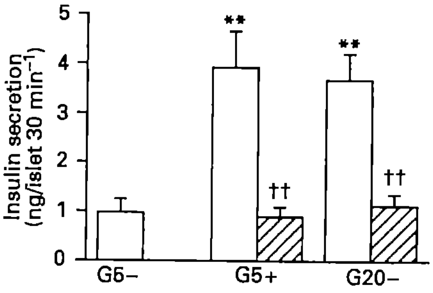

FIG. 3. Mean (SEM) insulin secretion in static incubation in the absence (open bars) or presence (hatched bars) of isoflurane. G5, G20 = glucose 5 or 20 mmol litre^{-1}; −, + = without or with glyceraldehyde 10 mmol litre^{-1}. **$P < 0.01$ compared with glucose 5 mmol litre^{-1}; ††$P < 0.01$ compared with incubation in the absence of isoflurane. $n = 7$ in all groups.

the control groups of islets, secretion increased significantly at 16, 18, 20 and 22 min ($P < 0.02$) compared with 10 min. In the experimental groups, insulin secretion remained significantly greater until 28 min compared with the value at 10 min ($P < 0.05$). In these islets, a change of the perifusion medium to glucose 20 mmol litre^{-1} with isoflurane at 30 min was associated with a rapid decline in insulin release, such that the values at 38 and 40 min were significantly different from that at 30 min ($P < 0.05$). In comparison with the control groups of islets which continued to receive glucose 20 mmol litre^{-1} alone, secretion was significantly less from 36 to 46 min ($P < 0.05$). The inhibition of insulin secretion by isoflurane in the experimental groups of islets was relieved when the buffer was changed back to glucose 20 mmol litre^{-1} alone. Insulin secretion in these islets subsequently increased, and from 58 to 70 min was significantly different from the value at 50 min ($P < 0.05$).

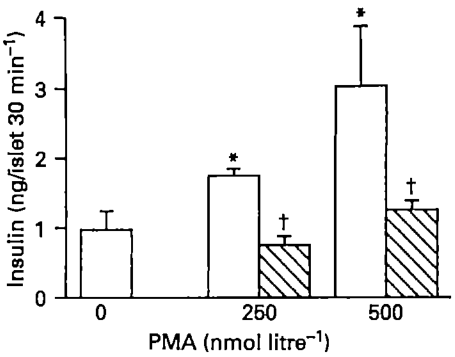

FIG. 4. Mean (SEM) insulin secretion in static incubation with glucose 5 mmol litre^{-1}, and increasing concentrations of phorbol myristate acetate (PMA) in the absence (open bars) or presence (hatched bars) of isoflurane. *$P < 0.01$ compared with glucose alone; †$P < 0.01$ compared with incubation at the same concentration of PMA in the absence of isoflurane. $n = 7$ in all groups.

Effects on glyceraldehyde-induced insulin secretion in static incubation (fig. 3)

In this experiment, insulin secretion in response to glucose 5 mmol litre^{-1} was 0.97 (0.27) ng/islet 30 min^{-1}. Secretion increased significantly—to 3.92 (0.73) ng/islet 30 min^{-1} ($P < 0.01$) with glyceraldehyde 10 mmol litre^{-1}, and to 3.67 (0.54) ng/islet 30 min^{-1} ($P < 0.01$) with glucose 20 mmol litre^{-1}. Both glyceraldehyde- and glucose-induced secretory responses were suppressed completely by addition of isoflurane at a vaporizer setting of 2%. Insulin secretion was 0.89 (0.20) and 1.12 (0.23) ng/islet 30 min^{-1}, respectively ($P < 0.01$) ($n = 7$ in all groups).

Effects on PMA-induced insulin secretion in static incubation (fig. 4)

Insulin secretion in response to glucose 5 mmol litre^{-1} (0.97 (0.27) ng/islet 30 min^{-1}) was stimulated significantly by PMA 250 and 500 nmol litre^{-1}, increasing to 1.75 (0.09) and 3.01 (0.83) ng/islet 30 min^{-1}, respectively ($P < 0.05$). Isoflurane inhibited the insulin secretion enhanced by the presence of both concentrations of PMA, to values of 0.75 (0.13) ng/islet 30 min^{-1} ($P < 0.01$) and 1.26 (0.13) ng/islet 30 min^{-1} ($P < 0.05$) ($n = 7$ in all groups).

Gas chromatography

The results of gas chromatography showed that using the 1% vaporizer setting for isoflurane produced a partial pressure of 0.38–0.46% isoflurane in the gas phase above the buffer in the microcentrifuge tubes during the static incubations. For the 2% vaporizer setting, the partial pressure after 1 min was 2.0%, decreasing to 1.33% at 10 min and was stable thereafter with a partial pressure of 0.89% at 20 and 30 min.

DISCUSSION

These experiments show clearly that isoflurane inhibited glucose-stimulated insulin secretion from isolated rat pancreatic islets of Langerhans *in vitro* in static incubations, although basal insulin secretion was not affected significantly. In this respect, our findings are in agreement with earlier results with the volatile anaesthetic agents halothane and enflurane [1,2]. The results of the perifusion experiment show that, after exposure of the islets to isoflurane, the islets remained capable of producing a further insulin secretory response to a stimulatory concentration of glucose. This important finding implies that isoflurane had a reversible inhibitory effect on insulin secretion, rather than impairing the functional ability of the islet cells by a toxic effect of the anaesthetic.

Methods for equilibrating volatile anaesthetics into incubation buffers for biological preparations similar to that used in the present study have been reported previously [8,9]. For clarity, the nominal settings dialled on the isoflurane vaporizer in our experiments have been stated. However, it is apparent that there are losses of isoflurane from the bubbling chamber to the microcentrifuge tubes. Therefore it was necessary to quantify the partial pressure of isoflurane in the vapour phase in equilibrium with the islet preparation. This was done using a standard method with gas chromatography [7] and showed that a nominal 2% vaporizer setting produced partial pressures which decreased initially and then stabilized for the remainder of the experiment.

The results of the present study show that isoflurane did not affect glucose transport across the cell membrane or interfere with the initiation of glucose metabolism, as insulin secretion stimulated at a more distal site by glyceraldehyde was nevertheless inhibited by isoflurane. This is in accordance with previous work using halothane and enflurane which suggested that these agents did not inhibit insulin secretion by interfering with glucose metabolism in the islet cells [2]. Also, the inhibitory effect of isoflurane on the stimulus secretion pathway must occur beyond the activation of protein kinases, as we have shown in the present study that insulin secretion promoted by the activation of protein kinase C by PMA was inhibited by the anaesthetic agent.

The effects of other drugs on secretion of insulin from pancreatic tissue have been documented. Morphine and endogenous opioid receptor agonists show disparate effects on insulin release, depending on the dose and substance used [10]. Clinically relevant concentrations of morphine in the nanomolar range stimulate insulin secretion *in vitro* [11]. A recent investigation showed that clinical concentrations of midazolam had no significant effect on insulin secretion from isolated rat islets of Langerhans [12].

Isoflurane is used increasingly in clinical practice [13] and has been introduced recently as an agent for sedation in intensive care. As we have shown that, *in vitro*, isoflurane directly inhibited insulin secretion from isolated pancreatic islets, it is important to know if the findings of the present investigation have any clinical relevance. It is possible that volatile agents may enhance the hyperglycaemia seen during surgery and critical illness. Suppression of basal values of circulating insulin cannot be excluded. A previous clinical study suggested that isoflurane may suppress the insulin response to a glucose load, but the dose of glucose used was excessive and unphysiological, and there was no comparison with a non-volatile anaesthetic [14]. Further studies are required to assess the effects of isoflurane on glucose-induced insulin release *in vivo*.

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EFFECTS OF FENTANYL ON THE RAT AORTA ARE MEDIATED BY ALPHA-ADRENOCEPTORS RATHER THAN BY THE ENDOTHELIUM

F. KARASAWA, V. IWANOV AND R. F. W. MOULDS

SUMMARY

We have assessed if fentanyl interacts with the endothelium to affect vessel tone. In the presence or absence of endothelium, fentanyl in concentrations greater than 10^{-7} mol litre^{-1} decreased the sensitivity of the rat aortic rings to phenylephrine, but fentanyl in smaller concentrations had no significant effect. Rings, with or without endothelium, and pre-contracted by phenylephrine were relaxed by fentanyl, and this relaxation was not inhibited by the opioid receptor antagonist, naloxone. Pretreatment of the rings with either fentanyl or phentolamine protected alpha-adrenoceptors from block by the alpha-adrenoceptor antagonist, phenoxybenzamine. We conclude that, in the rat aorta, fentanyl-induced relaxation was mediated by alpha-adrenergic receptors, and that the endothelium modulated, but did not mediate, this relaxation. (Br. J. Anaesth. 1993; **71**: 877–880)

KEY WORDS

Analgesics, intravenous: fentanyl, phenylephrine.

Fentanyl produces a relatively stable circulatory state. However, when used in large doses, as in anaesthesia for cardiac surgery, it decreases arterial pressure and vascular resistance [1, 2]. Fentanyl has been shown to dilate the isolated aorta of the rabbit and it has been proposed that this mechanism is mediated by adrenoceptors [3].

Since the endothelium was first recognized to have a key role in vasoreactivity, many reports have been published on endothelium-derived relaxing factor (EDRF). To our knowledge, however, there have been no reports on a possible role of EDRF in opioid-induced vascular relaxation.

The aim of the present study was to assess if endothelium is involved in the vasorelaxation induced by fentanyl, using the rat isolated aortic ring in both the presence and absence of endothelium.

MATERIALS AND METHODS

The study was approved by the Animal Ethics Committee of The Royal Melbourne Hospital. Sprague–Dawley rats of both sexes were killed by stunning and cervical dislocation. The descending thoracic aorta was removed carefully to protect the endothelial lining, residual blood was flushed out and the vessel cleared of adherent fat and connective tissue, then cut into transverse rings 3 mm long. Endothelial cells were removed mechanically in some aortic rings by inserting a triangular needle into the lumen and rolling the ring on a wet tissue. The rings were mounted on stainless steel hooks in 15-ml organ chambers for isometric force measurement (Grass FTO3C force transducer and Grass 7D or 79D polygraph), and were bathed in a physiological saline solution at 37 °C containing (mmol litre^{-1}): NaCl, 118; KCl, 4.8; $MgSO_4$, 1.2; $NaHCO_3$, 24; NaH_2PO_4, 1.2; $CaCl_2$, 2.5; glucose, 11. The buffer solution was gassed with 5% carbon dioxide in oxygen. The rings were equilibrated for about 1 h and stretched to a final resting tension of 1 g.

Before each experiment, the rings were contracted with the alpha-adrenergic agonist phenylephrine (10^{-7} mol litre^{-1} for denuded rings and 10^{-6} mol litre^{-1} for intact rings), which produced about 80% of the maximum contraction. The response of the rings to acetylcholine 10^{-6} mol litre^{-1} as an indicator of the presence or absence of endothelium was then tested. Rings with endothelium intact relaxed 81.1 (SEM 2.6)% with acetylcholine, and rings with endothelium denuded relaxed only 1.8 (2.6)%. In all experiments, each ring was also contracted with KCl 80 mmol litre^{-1} and subsequent responses were expressed as a percentage of this contractile response to KCl.

Effect of fentanyl on phenylephrine-induced contraction

Phenylephrine was administered cumulatively (from 10^{-9} to 10^{-5} mol litre^{-1}) into the organ bath to obtain concentration–contraction relationships before treatment with fentanyl. Selected randomly, some rings were incubated with fentanyl (10^{-7}, 10^{-6} or 10^{-5} mol litre^{-1}) for 30 min and then additional concentration–contraction relationships to phenylephrine were obtained. Other rings were used as time controls and were not treated with fentanyl. All concentration–contraction studies were separated by approximately 40 min.

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TABLE I. *Effect of fentanyl on the EC_{50} to phenylephrine (mean* (SEM)). *CCR = Corrected concentration ratio (see text).* * *Significant difference compared with values of 1.0 (see text)* ($P < 0.05$, *Student's* t *test*)

	n	EC_{50} ($\times 10^{-8}$ mol litre^{-1}) Before fentanyl	EC_{50} ($\times 10^{-8}$ mol litre^{-1}) After fentanyl	CCR
Endothelium present				
Fentanyl 10^{-5} mol litre^{-1}	6	57.3 (15.0)	222.4 (63.5)	7.91 (2.23)*
Time control	6	53.3 (7.3)	36.1 (10.5)	
Fentanyl 10^{-6} mol litre^{-1}	8	48.0 (24.9)	69.6 (39.8)	1.75 (0.27)*
Time control	8	46.9 (20.6)	40.7 (25.5)	
Fentanyl 10^{-7} mol litre^{-1}	7	47.9 (16.4)	43.3 (1.80)	1.32 (0.49)
Time control	7	53.3 (23.6)	46.6 (1.80)	
Endothelium absent				
Fentanyl 10^{-5} mol litre^{-1}	6	4.3 (1.5)	23.3 (5.8)	4.46 (0.83)*
Time control	6	4.4 (0.6)	5.3 (1.0)	
Fentanyl 10^{-6} mol litre^{-1}	8	3.1 (1.4)	11.1 (7.7)	2.07 (0.42)*
Time control	8	3.0 (1.3)	5.5 (4.0)	
Fentanyl 10^{-7} mol litre^{-1}	7	3.7 (1.1)	6.7 (1.9)	1.68 (0.71)
Time control	7	3.1 (1.2)	5.3 (2.2)	

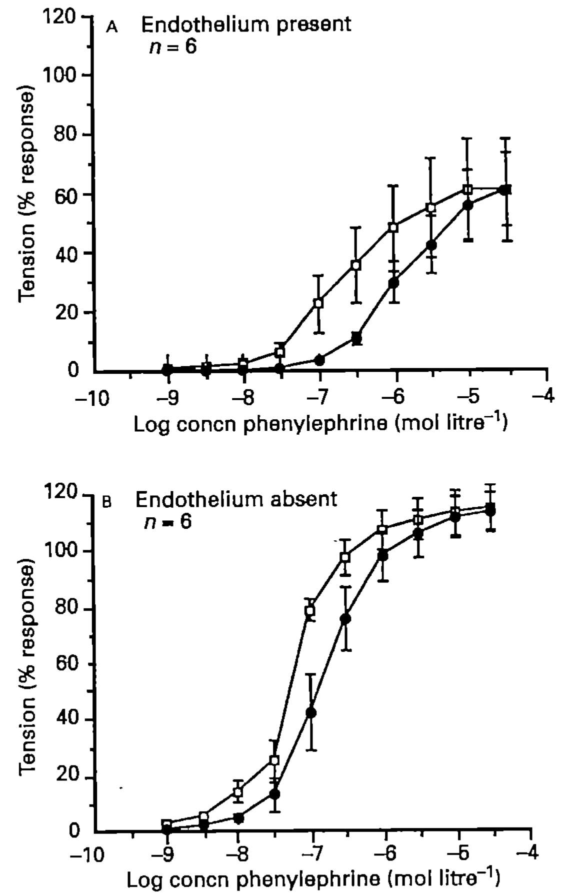

FIG. 1. Cumulative concentration–contraction relationships (mean, SEM) of the rat aortic ring with (A) and without (B) endothelium exposed to increasing concentrations of phenylephrine. Responses of control rings (□) and rings suspended in buffer solution containing fentanyl 10^{-5} mol litre^{-1} (●), expressed as percentage of the maximum response to a standard challenge, with KCl 80 mmol litre^{-1}.

For each concentration–contraction relationship, the estimated concentration producing 50% of the maximum response (EC_{50}) to phenylephrine was calculated using the least squares method for curve fitting to the sigmoid model [4]. The effect of fentanyl on the EC_{50} to phenylephrine was then expressed as a corrected concentration ratio (CCR), calculated as the ratio of the EC_{50} for phenylephrine in the presence and absence of fentanyl (corrected for the change in EC_{50} which occurred in the corresponding time control). If the drug had no effect on the EC_{50}, CCR was unity.

Effect of naloxone on fentanyl-induced relaxation

Rings with intact endothelium were contracted with phenylephrine 10^{-6} mol litre^{-1} and those without endothelium were contracted with phenylephrine 10^{-7} mol litre^{-1}. The tension induced by phenylephrine was expressed nominally as 100%. Fentanyl was then injected into the bath solution in cumulative concentrations (from 10^{-7} to 10^{-5} mol litre^{-1}) to obtain concentration–response relationships. Some preparations were incubated with naloxone 10^{-4} mol litre^{-1}, 20 min before the phenylephrine-induced contraction.

Alpha-adrenoceptor protection experiments

Concentration–contraction relationships to phenylephrine were obtained initially in both intact and endothelium-denuded rings. The rings were then washed and equilibrated in physiological saline solution alone for 40–50 min, pretreated with fentanyl 10^{-5} mol litre^{-1} or phentolamine 10^{-6} mol litre^{-1} for 30 min (controls received no fentanyl or phentolamine) and then all were treated with phenoxybenzamine 10^{-7} mol litre^{-1} for an additional 30 min. The phenoxybenzamine and other drugs (if present) were removed by five repeated washes, and the concentration–contraction relationship to phenylephrine determined again.

Statistical analysis

All results are expressed as mean (SEM). CCR values were compared with unity using paired Student's *t* test; for concentration–contraction relationships, two-way analysis of variance (ANOVA) was performed. Differences were considered statistically significant when $P < 0.05$.

Drugs

The following drugs were used: L-phenylephrine KCl, acetylcholine perchlorate, and naloxone (Sigma

Chemicals Co., St Louis, Mo); fentanyl citrate (Janssen-Cilag Pty Ltd, N.S.W., Australia); phentolamine (Ciba); phenoxybenzamine (Research Biochemicals Inc., U.S.A.). All drugs except phenylephrine were dissolved in distilled water. Ascorbic acid (10^{-4}) was used as an antioxidant in stock solutions of phenylephrine.

RESULTS

Effect of fentanyl on contractile response to phenylephrine

In endothelium intact rings the mean EC_{50} before treatment with fentanyl 10^{-5} mol litre^{-1} was 57.3 (15.0) × 10^{-8} mol litre^{-1} and the mean EC_{50} of the time controls was 53.3 (7.3) × 10^{-8} mol litre^{-1} (see table I). After incubation with fentanyl, the concentration–contraction relationship shifted significantly to the right (fig. 1) and the EC_{50} increased to 222.4 (63.5) × 10^{-8} mol litre^{-1}, producing a significant increase in the CCR of 7.91 (2.23) (table I). In endothelium-denuded rings, incubation with fentanyl 10^{-5} mol litre^{-1} again produced a significant rightward shift of the concentration–contraction relationship to phenylephrine (fig. 1) and the EC_{50} increased from 4.3 (1.5) × 10^{-8} mol litre^{-1} to 23.3 (5.8) × 10^{-8} mol litre^{-1}, producing a corresponding increase in CCR to 4.46 (0.83). Fentanyl 10^{-6} mol litre^{-1} also increased CCR significantly, to 1.75 (0.27) and 2.07 (0.42) in endothelium intact and endothelium-denuded rings, respectively, but fentanyl 10^{-7} mol litre^{-1} had no significant effect on the CCR in either case.

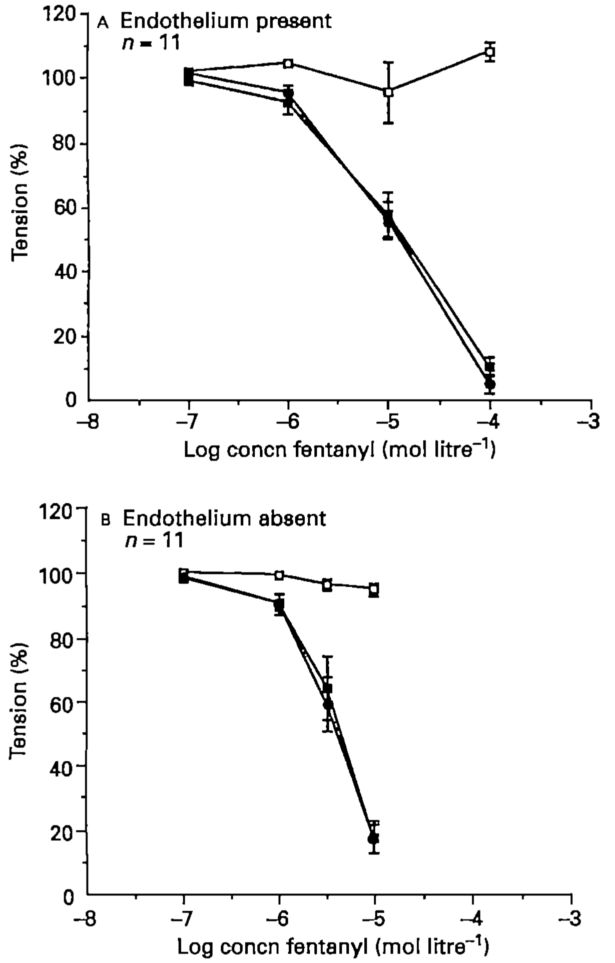

FIG. 2. Effects of the addition of increasing concentrations of fentanyl to aortic rings with (A) and without (B) endothelium, precontracted with phenylephrine 10^{-6} mol litre^{-1} (intact rings) or 10^{-7} mol litre^{-1} (denuded rings). Mean (SEM) responses to fentanyl alone (●), fentanyl in the presence of naloxone 10^{-4} mol litre^{-1} (■) and controls (□). Baseline tension = 100%.

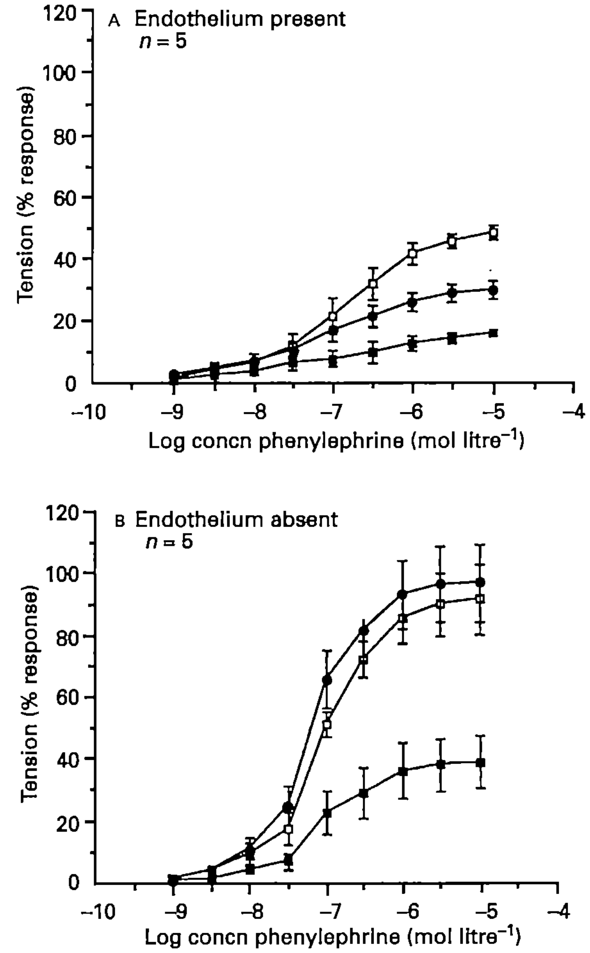

FIG. 3. Cumulative concentration–contraction relationships (mean, SEM) of rat aortic rings with (A) and without (B) endothelium exposed to increasing concentrations of phenylephrine. Rings were pretreated with either fentanyl 10^{-5} mol litre^{-1} (●) or phentolamine 10^{-6} mol litre^{-1} (□) and then phenoxybenzamine 10^{-7} mol litre^{-1}. Control rings (■) were not pretreated with either phentolamine or fentanyl before incubation with phenoxybenzamine. Contractions expressed as percentage of the maximum response to a standard challenge with KCl 80 mmol litre^{-1}.

Effect of naloxone

In both intact and denuded rings, fentanyl relaxed phenylephrine (10^{-6} mol litre^{-1} or 10^{-7} mol litre^{-1}, respectively) precontracted rings in a concentration-related manner (fig. 2). Pretreatment with naloxone 10^{-4} mol litre^{-1} had no significant effect on the fentanyl-induced relaxation (fig. 2).

Receptor protection

After incubation with phenoxybenzamine 10^{-7} mol litre^{-1} control rings showed markedly decreased contractile responses to phenylephrine in both endothelium-intact and endothelium-denuded rings (fig. 3), confirming irreversible alpha-adrenoceptor block with phenoxybenzamine. However, the rings pre-incubated with the alpha-adrenoceptor antagonist, phentolamine (10^{-6} mol litre^{-1}), before exposure to phenoxybenzamine showed significantly greater responses to phenylephrine after phenoxybenzamine washout than those in the control rings, indicating that phentolamine could protect the receptors from the action of phenoxybenzamine in both intact and denuded rings. Pre-incubation with fentanyl 10^{-5} mol litre^{-1} before exposure to phenoxybenzamine also increased significantly the contractile responses to phenylephrine after phenoxybenzamine washout in both intact and denuded rings (fig. 3), confirming that fentanyl, in common with phentolamine, protected the alpha-adrenoceptors from block by phenoxybenzamine.

DISCUSSION

We have shown that, in the rat aorta, fentanyl 10^{-5} and 10^{-6} mol litre^{-1} inhibited the contractile effects of phenylephrine in a concentration-dependent manner. We have also shown that naloxone did not inhibit the fentanyl-induced relaxation, and fentanyl had an effect similar to that of phentolamine in protecting alpha-adrenoceptors against block by phenoxybenzamine. Furthermore, we have found that, although the endothelium significantly altered responses to phenylephrine, the effects of fentanyl were similar in the presence or absence of the endothelium. Thus the endothelium acted as a modulator, but not a mediator, of the fentanyl-induced relaxation.

It has been reported [3] that fentanyl 10^{-6} mol litre^{-1} significantly dilated the helically cut rabbit aorta, where the endothelium seems to be partially reserved, and our results are consistent with this report. However Blaise and colleagues [5] reported that fentanyl 100 ng ml^{-1} (corresponding to approximately 3.0×10^{-7} mol litre^{-1}) had a small depressant effect on the contractile response to phenylephrine in the canine coronary ring with endothelium intact, and that it had no significant effect in the ring without endothelium. The differences between our results and theirs may be ascribed most easily to the use of different vessels from different species.

It has been reported that serum concentrations of fentanyl may be as great as 300 ng ml^{-1} (approximately 9.2×10^{-7} mol litre^{-1}) 1 min after injection of fentanyl 1 mg m^{-2} in patients [6]. Although fentanyl binds to serum proteins, the concentrations used in this study are likely to be similar to the maximum concentrations of fentanyl observed clinically.

The receptor protection experiments in this study confirmed that fentanyl had an alpha-adrenoceptor blocking effect. Furthermore, the fact that fentanyl protected the alpha-adrenoceptor in the presence or absence of endothelium is further confirmatory evidence that endothelial factors do not mediate the effects of fentanyl.

We conclude that fentanyl relaxes the rat aorta by antagonism of the alpha-adrenoceptor on vascular smooth muscle and that endothelium modulates, but does not mediate, this effect.

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IMPROVEMENT OF BRAIN ELECTRICAL ACTIVITY DURING TREATMENT OF PORCINE MALIGNANT HYPERTHERMIA WITH DANTROLENE

E. KOCHS, W. E. HOFFMAN AND J. SCHULTE AM ESCH

SUMMARY

Three months before this study, susceptibility for malignant hyperthermia (MH) had been tested in 15 pigs. In all pigs, MH was triggered by administration of 1% halothane. Brain electrical activity was examined during therapy of MH with and without administration of dantrolene. From the EEG, power densities in selected frequencies and the median frequency of the power spectrum were calculated. Therapy was started when severe respiratory changes were observed ($Pa_{CO_2} > 10$ kPa, mixed venous oxygen tension ($P\bar{v}_{O_2}$) < 4 kPa). At this time, heart rate exceeded 150 beat min^{-1}, mean arterial pressure (MAP) was less than 60 mm Hg and median frequency was less than 2 Hz. EEG was isoelectric ($n = 6$) or showed slow polymorphic delta-activity. For therapy, administration of all anaesthetics was terminated, 100% oxygen was delivered and ventilation was increased four-fold. Acidosis was treated by administration of sodium bicarbonate 2–4 mmol litre^{-1} kg^{-1}. Animals were allocated randomly to one of two groups: group I (control, $n = 7$) received no dantrolene; group II ($n = 8$) received dantrolene 2.5 mg kg^{-1} i.v. All variables were measured over a period of 60 min after therapy: EEG, HR and MAP were recorded continuously and blood-gas tensions, arterial potassium and glucose concentrations and pH were measured every 150 s. In group I (no dantrolene) minor, transient improvements in EEG activity were noted, but all animals died within 15–25 min after the start of therapy. In dantrolene-treated animals, EEG total power and median frequency increased within 5 min. The improvement in brain electrical activity occurred before any significant increases in MAP, Pa_{O_2} and $P\bar{v}_{O_2}$ or decreases in all Pa_{CO_2} or potassium plasma concentration. Our results indicate that dantrolene given for the treatment of a fulminant MH crisis helps to improve, not only haemodynamic state and metabolism, but also recovery of neuronal activity. (Br. J. Anaesth. 1993; 71: 881–884)

KEY WORDS

Anaesthetics, volatile: halothane. Anaesthetics, Intravenous: methohexitone. Drugs, intravenous: dantrolene sodium. Brain: electroencephalography. Malignant hyperthermia.

Initial deterioration in brain electrical activity may precede changes in haemodynamic and blood-gas variables during an acute episode of malignant hyperthermia (MH) [1]; when other signs are present, EEG recording may help to confirm an early diagnosis of MH [1]. During MH therapy, the extent and time course of recovery in brain electrical activity has not been delineated, but it is held generally that recovery of function of the central nervous system (CNS) follows improvement in haemodynamic, respiratory and metabolic state. Dantrolene is used for treatment of MH [2, 3]; in skeletal muscle, it inhibits release of calcium from the sarcoplasmic reticulum [4] and, as a result, MH-induced deterioration in haemodynamic and metabolic variables and sympathetic hyperactivity are reversed [2, 5]. It has been suggested that dantrolene decreases release of intracellular calcium in virtually all tissues [6]. There are no data so far on the effect of dantrolene on EEG characteristics. In this study, we have examined, in pigs, the time course of EEG recovery during MH treatment with dantrolene in relation to systemic haemodynamic, respiratory and metabolic variables.

MATERIALS AND METHODS

Our procedures were approved by the Veterinary Ethics Committee and were performed in accordance with the legal regulations for laboratory animals. We studied 15 animals from a colony of Pietrain pigs (21–38 kg, age 3–6 months) with genetic lines that have been maintained for the past 10 yr. When the animals were age 4–6 weeks, a test for MH-susceptibility was performed [1]: all pigs were challenged by exposure to 7% halothane in oxygen and animals responding within 1–2 min with rigidity of the pelvic limbs, abating after the immediate withdrawal of halothane, were classified as MHS. Rigidity was evaluated subjectively.

Each animal was fasted overnight, with free access to water. Pigs were premedicated with azaperon (Stresnil) 30–50 mg i.m. and metomidate hydrochloride (Hypnodil) 10 mg kg^{-1} i.m. Methohexitone 100–150 mg i.v. and vecuronium 0.1 mg kg^{-1} were given and the trachea was intubated. Mechanical

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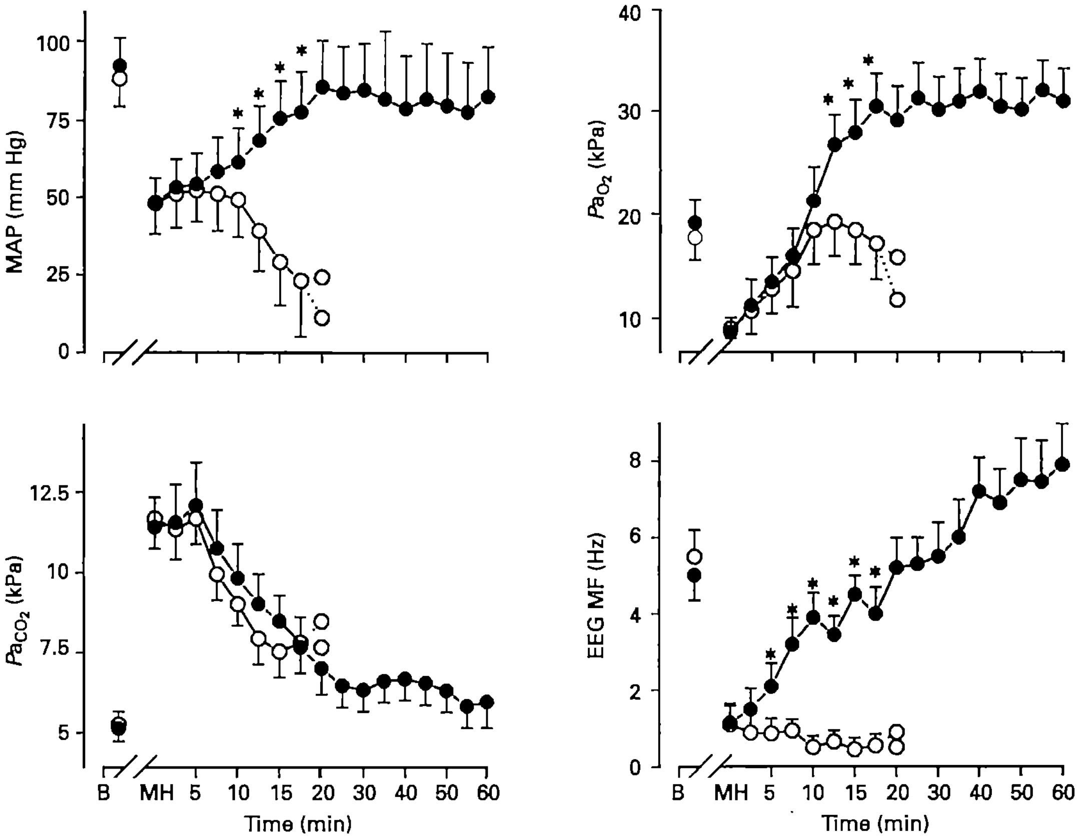

FIG. 1. Mean arterial pressure (MAP), arterial oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) tensions, and EEG median frequency (MF) at baseline (B), MH and after treatment without (group I: ○, $n = 7$) and with dantrolene (group II: ●, $n = 8$) in swine. *$P < 0.05$ compared with group I ($n = 2$ at time 20 min).

ventilation was controlled to maintain end-expiratory carbon dioxide tensions (PE'_{CO_2}) (Capnograph) of 4.4–4.9 kPa. Anaesthesia was maintained by methohexitone 25–40 mg h^{-1} and 50 % nitrous oxide in oxygen. In addition, fentanyl 10–25 µg kg^{-1} was given for surgical preparation. Anaesthesia was titrated to maintain a median EEG frequency of 4–5 Hz. MAP was monitored via a femoral artery catheter. A triple-lumen catheter (5-French gauge, Corodyn) was inserted into the pulmonary artery for measurement of pulmonary artery pressure (PAP). Body temperature was monitored via a thermistor at the tip of the catheter.

During surgery, Ringer's solution was given i.v. at a rate of 50–150 ml h^{-1} adjusted to maintain PAP 12–15 mm Hg. All pigs were paralysed with vecuronium 2–3 mg h^{-1}. After preparation, haemodynamic variables were allowed to stabilize for a period of 30 min.

Platinum needle electrodes for EEG recording were placed at a position corresponding to the vertex in humans (Cz) with linked earlobes (A1–A2) as reference and at parietal sites above the somatosensory projection areas (F1 and F2, corresponding to C3 and C4 in humans) *vs* a frontal reference (Fz). The electro-oculogram (EOG) was recorded from supra- and infraorbital leads. EEG and EOG were amplified (Biomed, non-electronics) and displayed on an eight-channel tape recorder (Store 7DS, Racal). The interelectrode impedances were maintained less than 5 kΩ (12 Hz). Bandpass for EEG and EOG recordings was set at 0.5–45 Hz. A commercially available software program (spike 2, Cambridge Electronic Design Ltd) was modified to perform Fast Fourier Transform on epochs of 5.26 s after digitization at a rate of 100 s^{-1}. Integrated EEG power was calculated for selected frequency bands as follows: delta: 0.5–3.9 Hz; theta: 4.0–7.9 Hz; alpha: 8.0–12.9 Hz; beta 1: 13.0–17.9 Hz; beta 2: 18.0–45 Hz. The median frequency was calculated from the total EEG power spectrum.

MH was induced by 1 % inspired halothane. The establishment of a fulminant MH crisis was determined according to the following criteria: $Pa_{CO_2} >$ 10 kPa, $P\bar{v}_{O_2} <$ 4 kPa. Simultaneous increases in heart rate and arterial potassium concentration and depression of MAP and EEG were taken as supportive evidence. Body temperature was greater than 40 °C. At this point the administration of all anaesthetics was terminated, 100 % oxygen was delivered and ventilation increased four-fold in both groups. Acidosis was treated by administration of sodium bicarbonate 2–4 mmol $litre^{-1}$ kg^{-1} in both groups. Group I ($n = 7$, control) received sham treatment whereas group II ($n = 8$) received dantrolene 2.5 mg kg^{-1} i.v. The experimental procedure and data collection were performed in a blinded manner. All observations were continued for 60 min after the start of therapy, at which time the animals were killed by an overdose of barbiturate.

In all animals, analog data (EEG, EOG, ECG, MAP, PE'_{CO_2}) were recorded continuously and stored on magnetic tape. Blood-gas analyses of mixed venous and arterial blood and measurement of serum

TABLE I. *EEG total power and median frequency (MF), heart rate (HR), central venous* Po_2 ($P\bar{v}_{O_2}$)*, arterial potassium concentration* ($[K^+]_a$) *and arterial pH after MH treatment (group I* (n = 7)*; group II* (n = 8*: treatment identical to group I plus dantrolene sodium 2.5 mg* kg^{-1} *i.v.)) over an observation period of 60 min.* $P < 0.05$*: compared with *MH; †group I. ‡*n = 2 *for all group I values at this time*

	EEG total power (% baseline)		EEG MF (Hz)		HR (beat min^{-1})		$P\bar{v}_{O_2}$ (kPa)		$[K^+]_a$ (mmol $litre^{-1}$)		pH_a	
Group:	I	II	I	II	I	II	I	II	I	II	I	II
MH	14 (5)	16 (7)	1.1 (0.6)	1.0 (0.7)	172 (25)	169 (23)	2.3 (0.5)	2.7 (0.7)	7.9 (1.2)	8.3 (1.3)	7.05 (0.11)	7.01 (0.12)
Time (min)												
5	15 (5)	22 (7)	1.2 (0.7)	2.1 (0.8)*†	169 (41)	155 (36)	1.7 (0.8)	2.9 (0.7)	8.3 (1.3)	8.4 (1.4)	7.06 (0.13)	7.05 (0.11)*
7.5	12 (6)	32 (9)*†	1.0 (0.5)	3.1 (1.1)*†	168 (39)	157 (38)	1.6 (0.9)	3.2 (0.7)	7.6 (1.1)	8.1 (1.4)	7.03 (0.14)	7.06 (0.12)*
10	9 (6)	48 (13)*†	0.8 (0.5)	3.9 (1.4)*†	171 (45)	146 (31)†	1.2 (0.7)	3.9 (0.9)*†	6.9 (1.3)	7.5 (0.9)*	6.99 (0.14)	7.24 (0.10)*†
20‡	5, 11	69 (18)*	0.5, 0.7	5.8 (1.7)*	168, 147	129 (32)*	1.2, 0.5	6.1 (1.2)*	5.7, 6.5	6.5 (1.0)*	6.79, 6.91	7.31 (0.12)*
40	—	92 (22)*	—	7.4 (2.1)*	—	115 (33)*	—	6.0 (1.2)*	—	5.7 (0.8)*	—	7.34 (0.10)*
60	—	91 (24)*	—	7.3 (2.3)*	—	109 (29)*	—	5.3 (1.5)*	—	4.9 (0.7)*	—	7.31 (0.13)*

concentrations of Na^+, K^+ and Cl^- were repeated every 2.5 min. Blood samples were obtained every 30 min for measurement of glucose.

All results are expressed as mean (SD). Comparisons were made by analysis of variance for repeated measurements, followed by *t* tests with Bonferroni corrections. Statistical significance was assumed at $P < 0.05$.

RESULTS

In all 15 animals, MH was diagnosed according to the criteria of $Pa_{CO_2} > 10$ kPa and $P\bar{v}_{O_2} < 4$ kPa. This occurred 43–68 min after the start of halothane administration and 18–33 min after the first signs of MH had been observed. In addition to diagnostic features of Pa_{CO_2} 11 (0.7) kPa and $P\bar{v}_{O_2}$ 2.5 (0.7) kPa, HR was increased to 171 (24) beat min^{-1}, MAP decreased to 49 (9) mm Hg, arterial blood concentration of potassium was 8.2 (0.9) mmol $litre^{-1}$ and plasma glucose concentration was 14 (2) mmol $litre^{-1}$. Total EEG power was decreased by 80–90 %, with a shift to polymorphic delta activity resulting in a median frequency less than 2 Hz. In six animals (group I: $n = 4$; group II: $n = 2$) (fig. 1), an isoelectric EEG was recorded. Body temperature was 41.3 (0.9) °C in both groups.

Pa_{O_2} improved with therapy in both groups (fig. 1). In group I (control) $P\bar{v}_{O_2}$ and arterial pH continued to decrease (table I) and all animals died within 25 min after the start of therapy. Body temperature did not change. In dantrolene-treated pigs (group II), all variables improved within 10 min (table I, fig. 1). Body temperature decreased and was 38.8 (1.1) °C at the end of the 60-min observation period.

During the fulminant MH crisis, the EEG was dominated by polymorphic delta-activity with a median frequency of 1.1 (0.6) Hz. In two animals in group I, initiation of therapy produced a transient increase in polymorphic delta- and slow theta-activity. However, this improvement was only transient, and deterioration was accompanied by a trend to lower median frequency (0.8 (0.5) Hz). An isoelectric EEG was recorded within 15–25 min after initiation of therapy.

In all dantrolene-treated pigs (group II), a significant improvement in EEG activity was noted 2.5–5 min before other physiological variables improved. EEG total power increased at 5 min with a shift to faster waves (median 2.1 (0.8) Hz) ($P < 0.05$). At the end of the observation period, recovery of EEG total power was almost complete, with dominant theta-alpha activity (6–10 Hz; median 7.9 (1.1) Hz).

DISCUSSION

These results show that MH therapy with dantrolene improved EEG activity and other physiological variables in MH-susceptible swine for up to 60 min after treatment. Initially, onset of EEG recovery preceded significant improvement in haemodynamic state and Pa_{CO_2}. Five minutes after dantrolene treatment, median EEG frequency was significantly greater than in control pigs, while haemodynamic and metabolic variables were still markedly abnormal. These findings indicate that dantrolene, in combination with supportive therapy, not only improved systemic haemodynamics and respiratory states, but also had a beneficial effect on neuronal function. The improvement in the EEG induced by dantrolene is related to inhibition of intracellular release of calcium [7, 8].

There is controversy on whether or not the central nervous system is primarily involved in the development of MH. Measurement of cerebral blood flow and metabolism indicate that these variables do not increase before systemic variables [9]. However, deterioration of EEG occurs 3–5 min before the development of significant cardiovascular or blood-gas changes [1]. This suggests that direct neuronal changes are affected in the early phase of MH.

It is possible that, during therapy, some early changes in EEG were mediated by components of the therapy such as withdrawal of anaesthetics, hyperventilation with 100% oxygen, treatment of acidosis and cooling. Initiation of therapy stabilized EEG activity in both groups. However, improvement in the EEG was significantly better in dantrolene-treated pigs in the first 5 min of treatment. This occurred at a time when Pa_{O_2} and other systemic variables did not differ between the groups. After 10 min of therapy, improvement in haemodynamic, respiratory and acid–base states may have contributed to the beneficial effects of dantrolene on the CNS.

Most studies of the effects of dantrolene have examined skeletal muscle, in which the aberrant metabolism during MH was first located. *In vivo* and *in vitro* studies indicate that, in skeletal muscle, dantrolene prevents the increase in mycoplasmic calcium concentration by preventing release from and augmenting uptake into the sarcoplasmic reticulum [10–14]. In conjunction with this effect on skeletal muscle, dantrolene facilitates reversal of aberrant haemodynamic, metabolic and sympathetic responses associated with MH [2, 3, 15]. It has been suggested that MH involves, not only skeletal muscle, but also the central and sympathetic nervous system, the myocardium and other tissues [16–19]. Inositol phosphate, a second messenger for intracellular calcium release, is increased in the myocardial and skeletal muscle of MHS swine and in skeletal muscle of patients susceptible to MH [18, 19]. This suggests that calcium release by sarcoplasmic or endoplasmic reticulum may be affected during MH in several tissues. Intracellular calcium may be released by increased inositol phosphates and antagonized by dantrolene [10, 11]. Studies on rat brain synaptosomes [7] and hippocampal pyramidal neurones [8] suggest that dantrolene blocks calcium release from microsomes without affecting reuptake. A direct effect of dantrolene in neuronal tissue would explain the initial improvement of EEG without significant changes in haemodynamic or respiratory variables.

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REVIEW ARTICLE

ANAESTHESIA OF ANIMALS FOR BIOMEDICAL RESEARCH

P. A. FLECKNELL

Anaesthetists trained to deal with human patients may be required to anaesthetize animal species as part of their involvement in biomedical research. Although the skills developed in clinical anaesthesia are of obvious relevance, several problems may be encountered when attempting to anaesthetize an unfamiliar species. This article reviews those areas which are of greatest practical importance to medical anaesthetists and discusses the ethical and legal aspects of research which involves the use of live animals.

ETHICAL AND LEGAL CONSIDERATIONS

The use of animals in biomedical research attracts considerable criticism from animal welfare groups. It is important that all those involved in such research projects are aware of the sensitive nature of this issue, and it is helpful to become familiar with the moral and ethical arguments which have been advanced on both sides of this debate. In Western Europe and North America, a broad consensus amongst research workers appears to have emerged, which accepts the need to use live animals in medical research, but seeks to reduce to a minimum any pain, suffering or distress which these animals may experience. This consensus is reflected in legislation such as the Animals (Scientific Procedures) Act, 1986 in the U.K., the Animal Welfare Act in the U.S.A., and the Council of Europe Directive within the E.C.

The Animals (Scientific Procedures) Act, 1986

Within the U.K., all research work which involves the use of living vertebrate animals is regulated by the Animals (Scientific Procedures) Act, (A(SP) Act), 1986, administered by the Home Office. The Act controls "regulated procedures" performed on "protected animals". A "regulated procedure" is any experimental or other scientific procedure which may cause the animal pain, suffering, distress or lasting harm. The "protected animals" are all vertebrates other than man, and the Act also includes protection for immature forms (fetuses and embryos) in addition to adult vertebrates. The Home Office definition of "pain, suffering, distress or lasting harm" is very broad, and includes physiological and psychological stress, disease, injury, disturbance to normal health and any significant discomfort. It is concerned both with short-term and long-term effects. Although death is also considered to be causing lasting harm, killing an animal by one of a number of specified techniques may remove the work from the control of the Act.

Personal Licences

The Act sets out to control "regulated procedures" in several ways. It controls the competence of individual research workers by means of "Personal Licences". A Personal Licence lists the techniques that may be carried out by the individual research worker and states the species of animal and whether anaesthesia is to be used for all, part or none of the techniques. The techniques listed on a Personal Licence are very specific and it is important not to carry out any procedure which is not specifically listed. The most important aspect of acting as the Personal Licence holder on a research project is that the licensee carries the primary responsibility for the care of the animals. These licences are granted to people who are believed to be competent to perform the procedures listed on the licence. Before a Personal Licence may be granted, the applicant will be required to attend a recognized training course, and will need to present evidence of his or her competence and relevant experience. Initially, the licence holder is unlikely to be competent to carry out all of the procedures without supervision, and a supervision clause will be added to the licence. When the licence holder is considered competent, the supervisor may request that the supervision condition is removed. When applying for a licence, the applicant is asked to state that they have read and understood the A(SP) Act, the Guidance Notes which are provided by the Home Office, and any relevant Codes of Practice.

Project Licences

Before a research worker who holds a Personal Licence can begin work which involves the use of animals, the research project must also have been authorized, by means of a "Project Licence". Full details of Project Licences are given in the Home Office Guidance Notes on the Act, but the following points are particularly important.

Project licensing is central to the operation of the A(SP) Act. The philosophical basis of the Act is to

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perform a cost–benefit analysis of research work. The cost to the animals in terms of adverse effects is weighed against the likely benefits to man or other animals. In order to perform this judgement, the Home Office require the Project Licence application to give details of the purpose of the work and provide a scientific justification for the proposed study. The Project Licence must also provide a detailed description of the procedures which are involved, an estimate of the number of animals that may be used, and an assessment of the potential adverse effects on the animals. This last assessment is referred to as the overall "severity" of the Project and it may be judged to be mild, moderate or substantial. A fourth category, unclassified, is reserved for studies which are carried out entirely under terminal general anaesthesia.

In many instances, the overall severity of a procedure can be reduced by applying carefully defined humane end-points. For example, rather than waiting until an experimentally induced condition results in the death of an animal, the animal could be humanely killed early in the course of the condition. In other circumstances, for example procedures involving surgical techniques, the severity of the procedure can be reduced by using analgesics and by providing a high standard of postoperative care. It is most important that a research worker becomes familiar with the detailed descriptions of the permitted procedures on the relevant Project Licence, and with the degree of pain, suffering or distress that the animals are permitted to undergo. Project Licences have a "severity band" which indicates this, and the licence will also detail what steps must be taken to minimize the adverse effects on the animal.

If it seems likely that the severity limit of a Project will be exceeded, the animal must either be killed, or the Home Office Inspector must be contacted.

The Personal Licensees involved with a Project should keep a record of all the procedures they undertake. Although it is the Project Licence holder's responsibility to report to the Home Office the details of all of the animals used on a Project, the records maintained by the Personal Licence holder will assist them in completing an accurate report.

Research workers may wish to visit another research institute in the U.K. to carry out a new technique, or to take part in a collaborative project. Before the visit, application must be made to the Home Office for permission to undertake work at the establishment. It is also important to ensure that the Personal Licence of the research worker is revised to incorporate any new procedures which may be undertaken and that the host institution's Project Licence covers the work that will be undertaken.

"Designated Premises" and the Certificate of Designation

Even after Project and Personal Licences have been granted, further controls are provided by the requirement that the work must only be carried out at a "designated place" which is specified on the Project and Personal Licences. The research institute is granted a Certificate of Designation which is held by some person in authority at the institute.

The Certificate holder is ultimately responsible for ensuring that all work carried out at the institute complies with the requirements of the A(SP) Act. To assist in fulfilling these statutory duties, the Certificate holder is required to appoint two "named persons": a "named person in day to day care" who is responsible for the health and welfare of all animals housed in the institute, and a "named veterinary surgeon" who is responsible for advising on animal health and welfare.

The implementation of the Act is also influenced by Home Office Codes of Practice. At present, only one of these, which sets out standards for housing and care of animals, has been published. This Code of Practice details the cage sizes, stocking densities, room temperatures, relative humidity and ventilation, staffing requirements and standards of building maintenance and design required for research animal units.

The Home Office Inspectorate

The administration and enforcement of the A(SP) Act is the responsibility of the Home Office Inspectors. Their role is to advise the Secretary of State on applications for Personal and Project Licences and Certificates of Designation. In effect, their advice is almost always accepted, hence they make the initial decision concerning the granting of licences. The Home Office Inspectors make unannounced visits to research laboratories to ensure that all of the conditions on Personal and Project Licences and on the Certificate of Designation are being fulfilled. The Inspectorate has immediate right of access to all areas of the premises. If an Inspector believes that an animal is undergoing excessive suffering, he may insist that it is killed immediately.

From the above description of the 1986 Act, its implementation may sound somewhat cumbersome and bureaucratic, and initial attempts at completing a licence application may seem difficult. However, in practice the legislation functions efficiently and advice on the drafting of licence applications is usually available within a research institute. Applicants are also normally advised to contact their Home Office Inspector at an early stage, to discuss any proposed research project.

Problems may arise when the anaesthetist is not directing the research project, but has been asked to provide specialized assistance with respect to the anaesthetic management of the research animals.It is important to realize that administering an anaesthetic is regarded as a research procedure, and the anaesthetist must have a Personal Licence to authorize their work. In addition, it is vital that the anaesthetist inspects carefully the Project Licence which authorizes the work, to determine the techniques for which authority has been granted. Certain procedures which may be regarded as routine clinical practice in a hospital setting require specific authority to be granted before they can be carried out; for example, the use of neuromuscular blocking agents is the subject of special controls in the U.K.

TABLE I. *Basic physiological data for laboratory animals*

Species	Ventilatory frequency (b.p.m.)	Tidal volume (ml)	Heart rate (beat min^{-1})	Blood volume (ml kg^{-1})	Body temp. (°C)	Body weight (kg)
Cat	26	30	150	85	38.6	3.0
Dog (Beagle)	25	150	100	80	38.3	15
Gerbil	90	—	260–600	—	39.0	0.09
Goat	20	325	80	70	39.4	50
Guineapig	120	2.5	155	75	38	0.5
Hamster	80	0.8	350	72	37.4	0.08
Mouse	180	0.15	570	75	37.4	0.030
Pig						
20 kg	18	420	80	70	39.0	20
200 kg	12	3800	65	65	39.0	200
Primate (Baboon)	35	50	150	75	39.0	10
Rabbit	50	20	220	70	38.0	3
Rat	90	1.6	350	58	38.0	0.2
Sheep	20	300	75	60	39.1	45

In general, it is advisable to discuss the proposed anaesthetic methodology with the local Home Office Inspector before commencing work. It is also good practice to prepare a written programme, both to assist in compliance with any legal requirements and to enable the methodology to be duplicated in the absence of the anaesthetist.

The Animal Welfare Act

In North America, the methods of regulation of research involving live animals are somewhat different, but are based on similar principles. In the U.S.A., the Animal Welfare Act sets out national standards. Within each research institute a local Ethics Committee reviews individual research proposals and determines if they comply with local and national requirements. In many institutes, the detail required in a submission to the Ethics Committee (usually referred to as the Animal Care and Use Committee) is similar to that of a U.K. Project Licence application. Although no separate Personal Licence system exists, most Ethics Committees require details of the relevant training and experience of the personnel who are involved in the project. In addition, many institutes now require new research workers to attend a training course before they are permitted to start their research work.

COMPARATIVE ANAESTHESIA

The most obvious practical problem that may be encountered by an anaesthetist who routinely deals with human subjects arises as a result of the small body size of some of the animals that are used in research laboratories (table I). Body size influences the type of equipment and the anaesthetic techniques that may be used, and the overall management of the animal during the perioperative period.

Anaesthetic equipment

TABLE II. *Equipment required for tracheal intubation in laboratory animals*

Species	Body weight	Tube diameter (o.d.) (mm)	Laryngoscope
Mouse	25–35 g	1.0	Purpose made laryngoscope [4]
Hamster	120 g	1.5	Purpose made laryngoscope [4]
Rat	200–400 g	1.8	Purpose made (12–16-gauge plastic cannula) laryngoscope [4]
Guineapig	400–100 g	1.5–2.5	Purpose made laryngoscope [4]
Rabbit	1–3 kg	2–3	Wisconsin size 0–1
	3–7 kg	3–6	
Cat	0.5–1.5 kg	2.0–3	MacIntosh size 1
	> 1.5 kg	3–4.5	
Dog	0.5–5 kg	2–5	MacIntosh size 1–4
	> 5 kg	4.0–15	
Primate	< 0.5 kg	—	Not reported
	0.5–20 kg	2–8	MacIntosh size 1–3
Sheep	10–90 kg	5–15	MacIntosh size 2–4
Pig	1–10 kg	2–6	Soper or Wisconsin size 1–4
	10–200 kg	6–15	

When dealing with animals of sizes comparable to those of adult humans and infants, standard anaesthetic apparatus can be utilized. Human paediatric breathing systems are particularly useful for animals weighing 1–10 kg and a Bain's circuit or Ayre's T-piece is the apparatus used most frequently. In species with a body weight less than 1 kg, the majority of anaesthetic breathing circuits, tracheal tubes and laryngoscopes designed for use in humans are unsuitable. Some purpose-made equipment can be purchased (see below), but in many instances apparatus must be constructed by the anaesthetist. Suitable circuits can be constructed from plastic or silastic tubing, and tracheal tubes from flexible "over-the-needle" catheters. Table II lists the approximate dimensions of tracheal tubes and laryngoscopes suitable for intubating the trachea of common laboratory animals. Techniques for intubation are described in several texts [9, 15, 25]. A particularly useful description of small rodent intubation and construction of a purpose-made

TABLE III. *Sedative/immobilizing agents for animals (dose (route)). †Fentanyl/fluanisone*

	Mouse	Rat	Hamster	Gerbil	Guineapig	Rabbit
Diazepam (mg kg^{-1})	5 (i.p.)	2.5 (i.p.)	5 (i.p.)	5 (i.p.)	5 (i.p.)	2 (i.v.)
Acepromazine (mg kg^{-1})	2.5 (s.c.)	2.5 (s.c.)	5 (s.c.)	5 (s.c.)	2.5 (s.c.)	1 (s.c.)
Hypnorm† (ml kg^{-1})	0.3 (i.p.)	0.4 (i.p.)	0.5 (i.p.)	0.5 (i.p.)	1 (i.p.)	0.5 (i.m.)
Xylazine (mg kg^{-1})	10 (i.p.)	10 (i.p.)	10 (i.p.)	5 (i.p.)	5 (i.p.)	5 (i.m.)
	Dog	Cat	Sheep/Goat	Pig	Primate	Ferret
Diazepam (mg kg^{-1})	—	—	2 (i.m.) 1 (i.v.)	1 (i.m.)	1 (i.m.)	2 (i.m.)
Acepromazine (mg kg^{-1})	0.1 (i.m.)	0.1 (i.m.)	0.1 (i.m.)	0.2 (i.m.)	0.2 (i.m.)	0.2 (i.m.)
Hypnorm† (ml kg^{-1})	0.2 (i.m.)	—	—	—	0.3 (i.m.)	0.5 (i.m.)
Xylazine (mg kg^{-1})	1–2 (i.m.)	1–3 (i.m.)	1 (i.m.) (sheep) 0.05 (i.m.) (goat)	—	—	—

laryngoscope is given by Costa and colleagues [4] and an alternative technique for the rat is illustrated clearly by Remie and colleagues [24].

After intubation, the animal may be allowed to breathe spontaneously, but mechanical ventilation allows more reliable and reproducible blood-gas variables to be maintained and this is required for many studies. Ventilators designed for human paediatric use are suitable for animals of 1–2 kg body weight and greater. Small animals require purpose-made apparatus, or adjustment of the anaesthetic breathing system to provide a controlled leak of ventilatory gas. Suitable ventilators are available from Harvard Apparatus Ltd (Fircroft Way, Edenbridge, Kent, U.K.; 22 Pleasant Street, South Natick, MA 01760, U.S.A.). Tidal volumes of approximately 10–15 ml/kg body weight and ventilatory frequencies from 80–100 b.p.m. (mice) to 10–20 b.p.m. (dog, sheep and pig) are usually required to maintain normocapnia. Monitoring of respiratory function presents several problems (see below).

Because of the technical difficulties associated with intubation, volatile anaesthetics are administered to small rodents usually via a face mask. This causes some problems with regard to scavenging of waste anaesthetic gases, and it is recommended that the concentric face mask system described by Hunter, Glen and Butcher [18] is purchased (Fluo-vac, International Market Supply, Dane Mill, Congleton, Cheshire, U.K.). Anaesthetic induction with volatile anaesthetics in small rodents is best carried out using a purpose-made induction chamber connected to a standard anaesthetic vaporizer and suitable gas scavenging equipment. In larger species such as rabbits, cats and dogs, anaesthesia may be induced using a face mask, but the patient may prove unco-operative. To prevent unnecessary stress, either induction should be achieved using injectable agents, or a potent sedative/tranquillizer should be administered as preanaesthetic medication (table III). The MAC value of the majority of volatile anaesthetics is similar in man and animals, and little difficulty will be experienced in judging depth of anaesthesia. An exception relates to nitrous oxide, which does not induce loss of consciousness in animals. It is therefore unacceptable to use an anaesthetic regimen consisting of nitrous oxide and a neuromuscular blocking agent alone.

Anaesthetic techniques

In most larger animals, superficial veins are readily accessible for drug administration and anaesthetic induction; venepuncture techniques are described by Tuffrey [27]. Catheters designed for use in man are suitable for most species, including small rodents. Skin thickness varies in different species, and in some animals it may be necessary to make a small scalpel incision before inserting a large over-the-needle type percutaneous catheter into a peripheral blood vessel. As in humans, prior application of EMLA cream facilitates venepuncture in conscious patients [12].

Because of the technical difficulties associated with venepuncture in small rodents, many injectable anaesthetic regimens have been developed which are administered by i.p. or i.m. injection. In general, the i.p. route is preferred to i.m. administration, as the irritant nature of some anaesthetics, coupled with the small muscle mass present in these animals, can lead to myositis [26]. A major disadvantage of both routes is that it is not possible to adjust the dose of anaesthetic according to the individual animal's response. This can lead to high anaesthetic mortality, particularly when agents with a narrow anaesthetic index are used, such as pentobarbitone. There is also a considerable variation in dose responses between animals of different strains, with sleep times varying by as much as 300 % in different strains of mice [20]. Published dose rates of anaesthetic agents, such as those listed in table IV, should therefore be used only as a general guide and, whenever possible, a single animal should be anaesthetized and the response assessed, before larger numbers of animals are used.

A second problem associated with the administration of relatively large dose rates of anaesthetics by the i.p. route is the very prolonged recovery times which result. For example, in the rat, several regimens produce 30–45 min of anaesthesia, but sleep times may extend to 120–180 min. During this period, the animal remains susceptible to hypothermia, respiratory failure or injury from cage mates if recovering in a group. To avoid this problem it may be helpful to consider use of reversible anaesthetic regimens [13, 17].

Species variation in drug responses. In addition to the variation in drug responses between individuals, different species vary in their response to some of the commonly used anaesthetics. Of particular relevance to anaesthetists is the very great species variation in response to ketamine and other dissociative anaesthetics. In man, ketamine is reported to produce good analgesia, and in the majority of non-human primates a cataleptic state with analgesia and immobilization is attained. The efficacy of this agent decreases in species with less cortical development. In the cat it is moderately effective, but ketamine rarely immobilizes pigs and sheep completely. In rodents, it is remarkably ineffective until doses which produce profound respiratory depression have been administered; at these dose rates, mortality may exceed 50%, and for this reason ketamine should not be used as the sole immobilizing agent. Most frequently, it is combined with a sedative such as a benzodiazepine, or an alpha$_2$ adrenergic agonist such as xylazine. In contrast to the effects of ketamine used alone, these combinations may produce surgical anaesthesia in many species.

Other species-specific drug responses of note include the effects of morphine, which should be administered in small doses to cats to avoid producing excitement, and alphaxalone–alphadolone which should not be administered to dogs, as the solubilizing agent in the commercial preparation can promote extensive histamine release in this species.

The depth of anaesthesia that can be provided by an anaesthetic before significant respiratory or cardiac depression ensues also varies in different species. Propofol is an effective anaesthetic in rats, mice, dogs, cats, pigs and sheep, but in rabbits severe respiratory depression occurs before the onset of surgical anaesthesia. Other commonly used human anaesthetic regimens are ineffective in some animal species, for example midazolam and other benzodiazepines do not produce unconsciousness in dogs and cats, and may cause agitation and excitement when administered by i.v. injection. Large doses of potent opioids such as fentanyl are effective analgesics, but unconsciousness is not achieved readily, many species developing excitement or respiratory arrest before consciousness is lost. Combinations of opioids and tranquillizers or sedatives are widely used, however, and produce safe and effective anaesthesia (table IV). As mentioned earlier, nitrous oxide does not produce loss of consciousness, so regimens based on high-dose opioids, nitrous oxide and a neuromuscular blocking agent are not acceptable.

Further information on species responses to individual anaesthetics has been reported by Green [14], Flecknell [9], Short [25] and Hall and Clarke [15]. It is also important to note that virtually all drugs which are in current clinical use have been tested for safety and efficacy in laboratory animals. Examination of the relevant literature often provides information on appropriate dose rates of many compounds.

Anaesthetic management

Animal health status. Laboratory species are susceptible to a wide range of diseases and a pre-anaesthetic clinical examination should be carried out to ensure that the subject is free from clinical signs of disease. Before major surgical procedures, routine haematological and biochemical evaluations should be undertaken. Normal values for these variables can be obtained in Loeb and Quimby [19] and Mitruka and Rawnsley [21]. Subclinical disease, for example respiratory infection, represents a considerable problem and it is advisable to discuss the health status of the animals with veterinary staff in the research animal unit. Most units will be undertaking some type of disease surveillance programme or quality assurance scheme, and will be able to provide advice on this topic. Working with animals that are free from disease is often essential if meaningful research data are to be obtained. It is also important to appreciate that some infectious diseases are zoonoses, and may represent a health hazard to personnel. This is a particular problem when working with non-human primates. Again, advice from veterinary staff should be obtained and local safety codes of practice should be adhered to.

Preoperative preparations. In order to allow time for preanaesthetic clinical evaluation to be undertaken, it is essential that animals are obtained 1–2 weeks before commencing any study. Local guidelines may exist, and these should be adhered to. Transport of animals from a supplier to the research laboratory is stressful, and animals require a period of acclimatization to adapt to their new surroundings. This acclimatization period also enables recording of body weight and food and water consumption—information which is extremely useful for monitoring postoperative recovery (see below).

Food should be withheld for 12–16 h before anaesthesia of dogs, cats, primates, ferrets, pigs and sheep. Fasting is unnecessary in small rodents and rabbits, unless upper gastrointestinal tract surgery is to be undertaken. Sheep and goats present particular problems with regard to anaesthetic management. These species have a stomach that consists of several sections, one of which, the rumen, acts as a fermentation chamber for the digestion of cellulose. During anaesthesia, normal oesophageal activity is suppressed and the gas which is produced accumulates in the rumen, causing massive distension of the abdomen. It is often necessary to relieve this distension by passage of a stomach tube.

TABLE IV. *Dose rates of anaesthetic, analgesic and related compounds for laboratory animals. Animals grouped: mouse, rat, hamster and gerbil; guineapig, rabbit, dog and cat; primates, pig, sheep and goats, ferret. Drugs listed in alphabetical order. Dose rates based on published data [14, 15] and clinical experience at the Clinical Research Centre, Harrow and the Comparative Biology Centre.*
** Sedation; ** immobilization; *** anaesthesia; ! severe respiratory depression may occur*

Drug	Mouse	Rat	Hamster	Gerbil
Alphaxalone/ alphadolone	10–15 mg kg^{-1} i.v.***	10–15 mg kg^{-1} i.v.***	150 mg kg^{-1} i.p.**/***!	80–120 mg kg^{-1} i.p.**/***!
Atropine	0.04 mg kg^{-1} s.c., i.m.	0.05 mg kg^{-1} s.c., i.m.	0.04 mg kg^{-1} s.c., i.m.	0.04 mg kg^{-1} s.c., i.m.
Buprenorphine	0.05–0.1 mg kg^{-1} s.c. 12 hourly	0.01–0.05 mg kg^{-1} s.c., i.v. 8–12 hourly	—	—
Butorphanol	1–5 mg kg^{-1} s.c. 4 hourly	2 mg kg^{-1} s.c. 4 hourly	—	—
Doxapram	5–10 mg kg^{-1} i.v.	5–10 mg kg^{-1} i.v.	5–10 mg kg^{-1} i.v.	5–10 mg kg^{-1} i.v.
Flunixin	2.5 mg kg^{-1} s.c., i.m. ?12 hourly	2.5 mg kg^{-1} s.c., i.m. ?12 hourly	—	—
Hypnorm (fentanyl+ fluanisone)	0.5 ml kg^{-1} i.p. */**	0.4 ml kg^{-1} i.m. or i.p. **	0.5 ml kg^{-1} i.m. or i.p. **	0.5 ml kg^{-1} i.m. or i.p. **
Hypnorm+ diazepam	0.4 ml kg^{-1} i.p. 5 mg kg^{-1} i.p. ***	0.3 ml kg^{-1} i.m. 2.5 mg kg^{-1} i.p. ***	1 ml kg^{-1} i.m. 5 mg kg^{-1} i.p. or i.v. ***	0.3 ml kg^{-1} 5 mg kg^{-1} i.p. ***
Hypnorm+ midazolam (2 parts water for injection+ 1 part Hyp.+ 1 part midaz.) (5 mg ml^{-1})	10 ml kg^{-1} i.p. ***	2.7 ml kg^{-1} i.p. ***	4 ml kg^{-1} i.p. ***	8 ml kg^{-1} i.p. ***
Ketamine+ medetomidine	75 mg kg^{-1} i.p. 1 mg kg^{-1} i.p.	75 mg kg^{-1} i.p. 0.5 mg kg^{-1} i.p.	—	—
Ketamine+ xylazine	150 mg kg^{-1} i.p. 10 mg kg^{-1} i.p. **/***!	90 mg kg^{-1} i.p. 10 mg kg^{-1} i.p. **/***	200 mg kg^{-1} i.p. 10 mg kg^{-1} i.p. ***	50 mg kg^{-1} i.p. 2 mg kg i.p. **
Morphine	2.5 mg kg^{-1} s.c. 2–4 hourly	2.5 mg kg^{-1} s.c. 2–4 hourly	—	—
Nalbuphine	4–8 mg kg^{-1} i.m. ?4 hourly	1–2 mg kg^{-1} i.m. 3 hourly	—	—
Naloxone	0.01–0.1 mg kg^{-1} i.p., i.v.	0.01–0.1 mg kg^{-1} i.p., i.v.	0.01–0.1 mg kg^{-1} i.p., i.v.	0.01–0.1 mg kg^{-1} i.p., i.v.
Pentobarbitone	45 mg kg^{-1} i.p. **/***!	45 mg kg^{-1} i.p. **/***!	50–90 mg kg^{-1} i.p. **/***!	60–80 mg kg^{-1} i.p. **/***!
Pethidine	10–20 mg kg^{-1} s.c. or i.m. 2–3 hourly	10–20 mg kg^{-1} s.c. or i.m. 2–3 hourly	—	—
Propofol	26 mg kg^{-1} i.v.	10 mg kg^{-1} i.v.	—	—
Thiopentone	30–40 mg kg^{-1} i.v. ***	30 mg kg^{-1} i.v. ***	—	—

Drug	Guineapig	Rabbit	Dog	Cat
Alphaxalone/ alphadolone	40 mg kg^{-1} i.v. **	6–9 mg kg^{-1} i.v. ***!	—	9–12 mg kg^{-1} i.v. *** 12–18 mg kg^{-1} i.m.
Atropine	0.05 mg kg^{-1} s.c., i.m.	0.05 mg kg^{-1} i.m.	0.05 mg kg^{-1} s.c., i.m.	0.05 mg kg^{-1} s.c., i.m.
Buprenorphine	0.05 mg kg^{-1} s.c. 8–12 hourly	0.01–0.05 mg kg^{-1} s.c. or i.v. 8–12 hourly	0.01–0.02 mg kg^{-1} i.m., s.c., i.v. 8–12 hourly	0.005–0.01 mg kg^{-1} s.c. or i.v. 8–12 hourly
Butorphanol	—	0.1–0.5 mg kg^{-1} i.v. 4 hourly	0.4 mg kg^{-1} s.c. or i.m. 3–4 hourly	0.4 mg kg^{-1} s.c. 3–4 hourly
Doxapram	5 mg kg^{-1} i.v.	2–5 mg kg^{-1} i.v.	2–5 mg kg^{-1} i.v.	2–5 mg kg^{-1} i.v.
Flunixin	—	1.1 mg kg^{-1} s.c., i.m. ?12 hourly	1 mg kg^{-1} per os daily	1 mg kg^{-1} s.c., daily for up to 5 days
Ketamine	100 mg kg^{-1} i.p. **	50 mg kg^{-1} i.m. **	—	20 mg kg^{-1} i.m. **
Ketamine+ medetomidine	40 mg kg^{-1} i.p. 0.5 mg kg^{-1} i.p.	25 mg kg^{-1} i.m. 0.5 mg kg^{-1} i.m.	—	—
Ketamine+ xylazine	40 mg kg^{-1} i.p. 5 mg kg^{-1} i.m. **/***	25 mg kg^{-1} i.m. 5 mg kg^{-1} i.m. ***	5 mg kg^{-1} i.v. 1–2 mg kg^{-1} i.v., i.m. ***	15 mg kg^{-1} i.m. 1 mg kg^{-1} s.c., i.m. ***
Morphine	2–5 mg kg^{-1} s.c. or i.m. 4 hourly	2–5 mg kg^{-1} s.c. or i.m. 2–4 hourly	0.5–5 mg kg^{-1} s.c. or i.m. 4 hourly	0.1 mg kg^{-1} s.c. 4 hourly
Nalbuphine	—	1–2 mg kg^{-1} i.v. 4–5 hourly	0.5–2.0 mg kg^{-1} s.c., i.m. 3–8 hourly	1.5–3.0 mg kg^{-1} i.v. 3 hourly
Naloxone	0.01–0.1 mg kg^{-1} i.p., i.v.	0.01–0.1 mg kg^{-1} i.m., i.v.	0.01–0.05 mg kg^{-1} i.m., i.v.	0.01–0.05 mg kg^{-1} i.m., i.v.

Hypnorm (fentanyl/ fluanisone)	0.65 ml kg^{-1} i.m. **	0.22 ml kg^{-1} i.m. *	0.1–0.2 ml kg^{-1} i.m. **	—
Hypnorm + diazepam	1 ml kg^{-1} i.m. 2.5 mg kg^{-1} i.p. ***	0.3 ml kg^{-1} i.m. 2 mg kg^{-1} i.p. or i.v. ***	—	—
Hypnorm + midazolam (2 parts H$_2$O + 1 part Hyp. + 1 part midaz.) (5 mg ml^{-1})	8 ml kg^{-1} i.p. ***	0.3 ml kg^{-1} i.m. +2 mg kg^{-1} i.v. or i.p. ***	—	—
Ibuprofen	10 mg kg^{-1} i.m. ?4 hourly	10 mg kg^{-1} i.v. ?4 hourly	5–10 mg kg^{-1} per os 24–48 hourly	—
Pentobarbitone	37 mg kg^{-1} i.p. **/***!	30–45 mg kg^{-1} i.v. ***!	20–30 mg kg^{-1} i.v. ***	25 mg kg^{-1} i.v. ***
Pethidine	10–20 mg kg^{-1} s.c. or i.m. 2–3 hourly	10 mg kg^{-1} s.c. or i.m. 2–3 hourly	10 mg kg^{-1} i.m. 2–3 hourly	10 mg kg^{-1} s.c. or i.m. 2–3 hourly
Propofol	—	10 mg kg^{-1} i.v.	5–7.5 mg kg^{-1} i.v. ***	7.5 mg kg^{-1} i.v. ***
Thiopentone	—	30 mg kg^{-1} i.v. ***	10–20 mg kg^{-1} i.v. ***	10–15 mg kg^{-1} i.v. ***

Drug	Primates	Pig	Sheep/goats	Ferret
Alphaxalone/ alphadolone	12–18 mg kg^{-1} i.m. **/*** 10–12 mg kg^{-1} i.v.***	6 mg kg^{-1} i.m. ** then 2 mg kg^{-1} i.v. ***	2.2 mg kg^{-1} i.v. (adult) 6 mg kg^{-1} i.v. (lamb)***	12–15 mg kg^{-1} i.m.**/*** 8–12 mg kg^{-1} i.v.***
Atropine	0.05 mg kg^{-1} i.m.	0.05 mg kg^{-1} i.m.	0.05 mg kg^{-1} i.m.	0.05 mg kg^{-1} i.m.
Buprenorphine	0.01 mg kg^{-1} i.m. 8–12 hourly	0.01–0.05 mg kg^{-1} i.m. 8–12 hourly	0.005–0.01 mg kg^{-1} i.m. 4–6 hourly	—
Doxapram	2 mg kg^{-1} i.v.	1–2 mg kg^{-1} i.v.	2 mg kg^{-1} i.v.	1–2 mg kg^{-1} i.v.
Flunixin	?2.5–10.0 mg kg^{-1} i.m. daily	?1 mg kg^{-1} s.c. daily	?1 mg kg^{-1} s.c. daily	—
Hypnorm (fentanyl/ fluanisone)	0.3 ml kg^{-1} i.m. **	—	— **	0.5 ml kg^{-1} i.m.
Ketamine	5–25 mg kg^{-1} i.m. */***	10 mg kg^{-1} i.m. **	20 mg kg^{-1} i.m. i.p. *	10–30 mg kg^{-1} **
Ketamine + diazepam	15 mg kg^{-1} i.m. 1 mg kg^{-1} i.m. **/***	10 mg kg^{-1} i.m. 2 mg kg^{-1} i.m. **	4 mg kg^{-1} i.v. 2 mg kg^{-1} i.m. or 1 mg kg^{-1} i.v.***	25 mg kg^{-1} i.m. 2 mg kg^{-1} i.m. ***
Ketamine + xylazine	10 mg kg^{-1} i.m. 0.5 mg kg^{-1} i.m. **/***	5 mg kg^{-1} i.m. 1 mg kg^{-1} i.m. */**	4 mg kg^{-1} i.v. 1 mg kg^{-1} (sheep) 0.05 mg kg^{-1} (goat)*/**	25 mg kg^{-1} i.m. 2 mg kg^{-1} i.m. ***
Methohexitone	10 mg kg^{-1} i.v. **/***	5 mg kg^{-1} i.v. ***	4 mg kg^{-1} i.v. ***	—
Morphine	1–2 mg kg^{-1} s.c. 4 hourly	up to 20 mg total dose i.m. 4 hourly	10 mg total dose i.m., s.c. 4 hourly	—
Naloxone	0.01–0.05 mg kg^{-1} i.v., i.m.	0.01–0.05 mg kg^{-1} i.v., i.m.	0.01–0.05 mg kg^{-1} i.v., i.m.	—
Pentobarbitone	5–15 mg kg^{-1} i.v. ***	30 mg kg^{-1} i.v. **/***	30 mg kg^{-1} i.v. ***	25–30 mg kg^{-1} i.v. ***
Pethidine	2–4 mg kg^{-1} i.m. 3–4 hourly	2 mg kg^{-1} i.m. 4 hourly	200 mg i.m. total dose 4 hourly	—
Propofol	—	2.5–3.5 mg kg^{-1} i.v.	3–4 mg kg^{-1} i.v.	
Thiopentone	15–20 mg kg^{-1} i.v. **/***	6–9 mg kg^{-1} i.v. ***	15 mg kg^{-1} i.v. ***	—

It is also essential to pass a tracheal tube in these species, to prevent inhalation of liquid rumen contents which are regurgitated during anaesthesia.

If it is intended that the animal recovers from anaesthesia, then equipment required for post-operative care should be prepared for use before commencing the experimental procedure (see below).

Handling and restraint. Restraint of the subject to allow easy induction of anaesthesia frequently presents difficulties when working with animals. Parallels may be drawn with human paediatric practice, in which stormy inductions can result because of a distressed and agitated patient. To avoid this problem, it is strongly recommended that the assistance of an experienced animal technician is obtained. Training in correct animal handling techniques should be sought and, although practical instruction is essential, it may be helpful to consult publications such as those by Anderson and Edney [1] and Tuffrey [27]. To avoid the need for excessive physical restraint, use can be made of anaesthetic induction chambers or a tranquillizer or sedative can be administered before induction of anaesthesia.

Anaesthetic maintenance

The general principles of monitoring and supporting vital body functions during anaesthesia apply equally to animals and man, but maintenance of body temperature is of special importance when anaesthetizing small rodents. The techniques used when managing human paediatric patients may be used, and a range of purpose-made heating pads and blankets are available commercially. Body temperature can be monitored using standard human electronic thermometers, although the probe size of these devices is usually too large for mice, and specially designed probes are needed to monitor temperature in this species.

Monitoring of respiratory function is simple in large animals, and respiratory monitors, capnographs and respirometers designed for human use can be used successfully. Small animals (< 1 kg) present special problems; for example, the sampling volume of a capnograph frequently exceeds the minute volume of these animals. Similarly, the small tidal volumes may fail to trigger thermistor devices used to monitor ventilatory frequency. Capnograph probes and respiratory monitors that are provided with a mount for incorporation into a standard diameter anaesthetic circuit may introduce excessive equipment deadspace and should be modified before use in small animals. The most useful monitoring device is a pulse oximeter, which can be used for rats (positioned on the hind foot pad), rabbits (on the ear, tongue or nose) and in a variety of sites in larger species. It is important to assess a manufacturer's instrument before embarking on a study, as considerable variation in performance is encountered.

Monitoring of blood-gas variables in laboratory species is feasible, providing that an analyser capable of accepting small sample volumes is used. Percutaneous arterial cannulation is practicable in rabbits and larger species, but surgical exposure of vessels is required in rats and guineapigs. In small animals, it is advisable to replace the blood withdrawn for analysis with whole blood from a donor animal. Cross-matching is rarely practicable, but initial transfusion reactions are rare. As with man, blood should be collected from a donor animal into ACD. Information on appropriate storage times of blood from laboratory species is not available and it is advisable to obtain blood for transfusion shortly before it is required.

General principles of fluid therapy apply and replacement fluids such as plasma volume expanders and crystalloid solutions can be used in all species. Blood volume is generally 60–70 ml kg^{-1}, so there may be practical problems related to the very small infusion rates required by small animals.

Monitoring of cardiovascular function can be carried out using techniques similar to those used in man. Invasive arterial pressure monitoring is practicable in most species, although problems may be encountered when attempting arterial cannulation in very small animals such as mice. In larger species, percutaneous catheterization enables routine monitoring of arterial pressure. Non-invasive monitoring equipment may be used in cats, dogs and larger animals, but it is important to assess the performance of different manufacturers' equipment, as the ability to detect low amplitude signals varies considerably. Specially designed apparatus is available to monitor arterial pressure in small rodents via a cuff placed around the tail.

The ECG can be monitored using standard techniques, although some apparatus designed for use in man will not detect the low amplitude signals from small animals. A further complication arises from the rapid heart rates of some species. Monitoring devices for use in man often have a detection limit of 300 beat min^{-1}, and this rate is exceeded in small rodents and rabbits. A monitor specifically designed to overcome these problems is available (Silogic EC60, Silogic Design Ltd, Enterprise House, 181–189 Garth Rd, Morden, Surrey, U.K.).

Special problems

Some problems unique to the research environment may be encountered. One major issue concerns the potential interaction between the anaesthetic regimen used and the research design. When an anaesthetic regimen is formulated, it is important that the experimental design is considered in conjunction with the pharmacology of the anaesthetic agents, so that interactions may be minimized. This may require an extensive review of the relevant literature, but is essential if serious problems are to be avoided. It is important to appreciate that previous investigators may not have considered this problem adequately, and adoption of an anaesthetic regimen from a previously published study does not guarantee that it is appropriate for the present purpose.

A requirement of some research projects is the provision of stable, long lasting anaesthesia, with minimal depression of the circulatory or respiratory systems. Several compounds unfamiliar to human anaesthetists, such as urethane [7] and chloralose, may be used for this purpose. Although the claims made for these agents are well established by historical precedence, it is advisable to review the existing literature critically before accepting them without question.

Anaesthetists may occasionally be asked to assist in studies involving non-mammalian species, such as fish, reptiles, birds and amphibia. These species often respond very differently to anaesthetic regimens that are satisfactory in mammals, and it is strongly advised that specialist advice is sought before anaesthetizing these animals.

Postoperative care

As in human anaesthetic practice, monitoring procedures and supportive therapy should be continued into the postanaesthetic recovery period. It is important to appreciate that the extensive nursing support available in human clinical practice may not be available in a research animal unit. Responsibility for the provision of postoperative care rests with the anaesthetist, and this may require the establishment of a specialized recovery area. For small animals, a human infant incubator can be used to provide a suitable environment. Assistance should be sought from staff in the facility to set up recovery pens for larger species. Although all animals require nursing attention during recovery, the response to physical contact varies considerably. Companion animal species which have become accustomed to handling, such as dogs and cats, respond positively to attention from their handlers, but other species such as mice and guineapigs may find such attention stressful.

It is important to monitor fluid and food intake and body weight in the postoperative period and provide supportive therapy as necessary. In small animals, supplementary fluids can be provided by administering 4% glucose–0.18% saline or 0.9% saline by the s.c. or i.p. routes, the initial dose being administered before recovery from anaesthesia. Larger species can receive i.v. therapy, but special measures may be required to prevent the animal interfering with infusion cannulae. If prolonged drug or fluid therapy is required, it may be appropriate to implant an indwelling catheter, which can be tunnelled to emerge between the shoulders at the base of the neck, so that the animal cannot interfere with it. Techniques for cannulation have been reviewed by Desjardins [6].

ASSESSMENT AND ALLEVIATION OF POSTOPERATIVE PAIN

The provision of adequate pain relief following surgical procedures is of special importance. As animals are unable to communicate directly with man, problems of pain assessment similar to those encountered with neonatal humans arise. Two approaches to the recognition of pain have been suggested: either anthropomorphic criteria may be used, based on a knowledge of the degree of pain experienced by humans after comparable surgical procedures, or methods of assessment based on observations of the animal's behaviour can be developed. An anthropomorphic approach has serious limitations, as it requires uncritical assumptions to be made, not only that pain occurs in the same circumstances in animals and man, but also that pain intensity, duration and analgesic requirements are identical. Knowledge of the individual variations which occur between human patients indicates that such assumptions are untenable. Another limitation of this approach is that it precludes any comparative assessment of different types of analgesic regimens.

The second approach of attempting to assess changes in behaviour that may be pain related has many similarities to techniques used for pain assessment in human neonates and infants. Several schemes for pain assessment and pain scoring have been published [2, 22], but attempts to use them to assess pain have had limited success [3]. Recently, however, studies in which trained observers completed a linear analogue pain score on behalf of their veterinary patients have proven encouraging [23]. All these scoring systems require the assessor to have a good knowledge of the normal behaviour of the animal species concerned, and preferably to be familiar with the normal behaviour of the individual animal. This requires considerable experience, and it is often advisable to seek the advice of a laboratory animal veterinary surgeon or experienced animal technician when attempting such an assessment. It is important to note that many laboratory rodents are most active at night, and an assessment carried out during the light phase of their photoperiod may not be particularly useful. As an alternative to the relatively subjective approach of behavioural observations and scoring of clinical appearance, the use of food and water intake and body weight as indices of postoperative pain have been evaluated. Initial investigations suggest that these variables are depressed following surgery, and that analgesic agents reduce the magnitude of this effect [11]. Body weight is a simple variable to monitor, and may provide a reasonably reliable indicator of the efficacy of analgesic therapy in small rodents.

Management of acute pain in animals

The methods available for the management of acute postoperative pain in animals are similar to those which are used in man. Centrally or peripherally acting analgesics may be administered systemically or techniques involving the use of local anaesthetics may be used. The application of supporting bandages or other means of protecting and immobilizing damaged tissues should also be considered. Selection of a particular regimen of treatment varies depending upon the nature of the pain, its cause and its estimated severity and duration.

The majority of animals which have undergone surgical procedures require opioids to produce effective pain relief. All the opioids available for clinical use in man have undergone testing for efficacy in laboratory animals and hence dose regimens can be suggested on the basis of these data [8]. The efficacy of these dose regimens in treating clinical pain remains uncertain, as the agents were assessed using experimental analgesiometry (for example the tail flick test). As our understanding of postoperative pain in animals improves, it should be possible to revise the dose rates listed in table IV.

In research animal facilities, it is rarely possible to provide the level of nursing care available in human clinical practice. This creates problems in providing prolonged periods of pain relief, as most opioids require repeated administration at 3–4 h intervals. One approach is to use buprenorphine, which has been shown to have a long duration of action (6–12 h) in several species (rat [5], rabbit [10] and pig [16]). An alternative approach is to adapt the technique of continuous infusion of opioids which has been developed in humans. In animals, opioids can be administered continuously either via i.v. fluids administered via a giving-set, or by bandaging a portable, battery-operated syringe driver to the animal (e.g. Graseby Dynamics MS16). Prolonged analgesia can also be produced by extradural morphine, although at present this technique has been used clinically only in larger species such as the dog, pig, sheep and horse. The undesirable side effects of opioids that are of concern in man must also be considered when administering these compounds to animals, but in general they are of considerably less clinical significance. Respiratory depression is perhaps the most serious consequence of overdose with opioids in man. This side effect may be seen occasionally in animals if large doses of morphine or pethidine are administered, or if potent μ agonists such as fentanyl or alfentanil are used. Significant respiratory depression occurs rarely after the use of normal clinical doses of morphine and pethidine, and has yet to be reported as a problem after administration of mixed agonist–antagonist drugs such as buprenorphine, nalbuphine and butorphanol.

Non-steroidal anti-inflammatory drugs are of use in the management of mild to moderate pain in animals, and may be of particular value in circumstances in which the use of opioids is contraindicated because of the requirements of a particular experimental procedure. Some recently introduced NSAID, such as flunixin and carprofen, have an efficacy which may approach that of some opioids, and these compounds are currently undergoing clinical evaluation.

Local anaesthetics such as bupivacaine may be used in the same way as in man, to provide local nerve blocks, for example after thoracotomy.

As in man, the requirement for postoperative analgesics rarely exceeds 72 h, and in most instances provision of pain relief for 24–48 h appears adequate.

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SHORT COMMUNICATION

COMPARISON OF PROPOFOL WITH ENFLURANE DURING HYPOTENSIVE ANAESTHESIA FOR MIDDLE EAR SURGERY

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SUMMARY

Forty patients undergoing middle ear surgery were allocated randomly to receive propofol induction and maintenance, or thiopentone induction and enflurane maintenance for anaesthesia. Both groups also received fentanyl, alcuronium, nitrous oxide and oxygen. If this did not reduce systolic arterial pressure to 70 mm Hg, labetalol, glyceryl trinitrate (GTN), or both, was administered. Fifteen control patients had enflurane anaesthesia without hypotension. Pre- and postoperative psychometric tests were performed in all groups. The propofol group received significantly more labetalol ($P = 0.014$*) and GTN (*$P = 0.004$*) than the enflurane group. There was a greater increase in reaction times after operation in the study groups (*$P < 0.05$*) compared with controls. There was no difference between the propofol and enflurane groups in control of arterial pressure, recovery from anaesthesia or psychometric testing.* (Br. J. Anaesth. 1993; **71**: 895–897)

KEY WORDS

Anaesthetics, intravenous: propofol. Anaesthetics, volatile: enflurane. Anaesthetic techniques: hypotensive.

Propofol is suited ideally for use by continuous infusion because of its minimal cumulative effect, with rapid recovery of consciousness and some reduction in arterial pressure. These properties suggest that continuous i.v. infusion of propofol may be useful for middle ear surgery, for which reduction in arterial pressure is often used to provide good operating conditions [1] and the duration of surgery may be variable. Propofol also reduces cerebral blood flow, cerebral metabolic rate for oxygen and intracranial pressure [2]. The decrease in cerebral metabolic rate may protect the brain during ischaemia [3, 4] and this may be of value during hypotensive anaesthesia.

We have compared the suitability of a continuous i.v. infusion of propofol with enflurane as part of a hypotensive anaesthetic technique for middle ear surgery. The effect of anaesthesia on postoperative cognitive function was measured to determine if propofol conferred some cerebral protection during hypotensive anaesthesia.

METHODS AND RESULTS

After obtaining approval by the Hospital Ethics Committee and written consent, we studied 40 patients (ASA grades I and II, aged 18–65 yr) requiring anaesthesia for middle ear surgery. The patients were allocated randomly to one of two groups: propofol induction and maintenance, initially 12 mg kg^{-1} h^{-1} reducing to 6–9 mg kg^{-1} h^{-1} after 10 min, fentanyl, alcuronium and 70 % nitrous oxide in oxygen (group 1); or thiopentone induction followed by maintenance with enflurane, fentanyl, alcuronium and 70 % nitrous oxide in oxygen (group 2). A control group, comprising 15 patients undergoing ENT operations not requiring hypotensive anaesthesia or significant postoperative analgesia, received thiopentone, fentanyl, alcuronium and enflurane.

Papaveretum 10–20 mg and prochlorperazine 12.5 mg were given i.v. 1 h before induction of anaesthesia. Anaesthesia was induced with propofol approximately 2 mg kg^{-1} or thiopentone 4–7 mg kg^{-1} titrated to effect, and analgesia was provided with fentanyl 2 μg kg^{-1}. All patients received alcuronium 0.2–0.3 mg kg^{-1} to facilitate tracheal intubation and their lungs were ventilated to maintain normocapnia. Arterial pressure (Datascope Accutorr) and heart rate were recorded every 1 min for 5 min and then every 5 min throughout anaesthesia and recovery.

The aim in both groups was to produce a systolic arterial pressure of 70 mm Hg within 10 min of induction and to maintain it at this value during surgery. If the desired hypotension was not achieved, labetalol was given i.v. according to a standard procedure and, if necessary, nitroglycerin (GTN) was infused at a rate of 25 μg min^{-1} increasing in steps of 25 μg min^{-1} until the desired pressure was achieved.

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TABLE I. *Operations performed (number (number who had psychometric testing)), doses of labetalol and nitroglycerin used and scoring in the psychometric tests (mean (SEM)) in the propofol, enflurane and control groups. CFF = Critical flicker fusion. Significant differences*: **$P < 0.05$*, ***$P < 0.01$*, *compared with propofol group*; †*$P < 0.05$ compared with both study groups*

	Propofol	Enflurane	Control
Operation			
Mastoid operation	8 (6)	8 (7)	
Tympanoplasty	7 (6)	8 (6)	
Stapedectomy	1 (1)	2 (1)	
Tympanotomy	4 (3)	2 (2)	
Labetalol used	(n = 18)	(n = 12)	
(mg)	53.9 (38.3)	37.1 (26.5)*	
Nitroglycerin used	(n = 18)	(n = 11)*	
(mg)	4.25 (3.45)	1.88 (1.22)**	
Concentration—digit			
Before op.	6.7 (1.4)	6.8 (1.2)	7.3 (1.39)
After op.	6.8 (1.6)	7.3 (1.0)	7.4 (1.24)
Concentration—month			
Before op.	16.2 (7.5)	17.1 (8.6)	20.6 (11.11)
After op	16.2 (6.9)	17.4 (10.6)	18.6 (9.22)
Memory			
Before op.	41.8 (8.3)	42.7 (6.8)	42 (6.73)
After op.	39.5 (7.4)	39.2 (5.00)	39.4 (6.25)
CFF—ascending			
Before op.	28.2 (3.5)	27.4 (4.3)	25.6 (2.32)
After op.	27.8 (3.2)	26.3 (5.1)	25.2 (3.09)
CFF—descending			
Before op.	28.3 (4.6)	27.0 (3.9)	28.2 (2.83)
After op.	27.5 (4.3)	25.0 (4.0)	27.1 (3.93)
Reaction time			
Before op.	246.4 (40)	249.2 (25.4)	243.9 (18.7)
After op.	265.2 (46.2)	268.6 (31.0)	247.5 (21.81)†

At the end of surgery, residual neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrronium 0.5 mg. The ease of control of arterial pressure was graded by the anaesthetist and the control of operative bleeding by the surgeon as good, adequate or poor. Postoperative analgesia was provided with oral paracetamol; prochlorperazine was prescribed for nausea.

Tests of cognitive function were performed before operation and 20–22 h after operation. These tests were carried out in the same environment, at the same time of day and by the same investigator, allowing a short period of practice before testing. The whole procedure lasted 30–45 min. Two tests of concentration were used: digit span, in which the patient was asked to repeat a series of numbers from three to nine characters in length and the time taken to recite the months of the year backwards. Learning ability and recall were tested using the Kendrick picture recall cards. A second set of cards was used for the postoperative test. Ascending and descending Critical Flicker Fusion was tested. A reaction time test measured the speed of response to a light being switched on at random frequency for a 10-min period.

Cardiovascular data were analysed using analysis of variance and Fisher's exact test as appropriate. The Mann–Whitney U test was used to compare the results of psychometric testing.

The complete groups and the subgroups which had psychometric testing had similar age and sex distributions. There was a similar distribution of operations in the two test groups (table I).

The average maintenance dose of propofol was 8.7 (SD 2.07) mg kg^{-1} h^{-1} and the average maintenance concentration of enflurane was 1.35 (0.30)%. The duration of anaesthesia was similar in the test groups, but shorter in the control group (propofol 99.8 (28.1) min; enflurane 106.5 (39.0) min; control 34.3 (8.0) min) ($P < 0.001$). There was no difference in immediate recovery times between the test groups.

There was no difference between test groups regarding ease of control of arterial pressure during operation or operating conditions. Significantly more labetalol was needed ($P = 0.014$) and GTN was used more frequently ($P = 0.031$) and in greater dosage ($P = 0.004$) in the propofol group.

In the enflurane group there were greater decreases from baseline systolic arterial pressure at 6–10 min ($P = 0.022$) and 11–30 min ($P = 0.008$) and from baseline diastolic arterial pressure at 6–10 min ($P = 0.022$) and 11–30 min ($P = 0.002$). At 11–30 min, heart rate was greater in the propofol group ($P = 0.009$).

There was a greater increase in reaction time from the preoperative to the postoperative test in both the propofol ($P < 0.05$) and enflurane groups compared with the control group (table I).

COMMENT

Anaesthetics that decrease cerebral oxygen consumption ($CMRo_2$) may protect the brain during ischaemia and improve neuronal outcome by decreasing cerebral oxygen demands [3]. Propofol has been shown to suppress brain electrical activity, $CMRo_2$ and cerebral blood flow (CBF) [2]. Cats receiving propofol and subjected to a period of profound hypotension causing incomplete global ischaemia had a better recovery of CBF, extracellular fluid ionic homeostasis and EEG activity compared with halothane controls, but this was not associated with demonstrably better histological outcome [4]. Similar studies in rats comparing propofol with nitrous oxide–fentanyl showed improved neurological outcome and brain histopathology which was independent of changes in plasma glucose [5]. Studies comparing halothane with propofol have not shown any difference in cerebral protection between the agents [6], but halothane has been shown to have a cerebral protective effect compared with nitrous oxide [3].

In this study there was a deterioration in psychometric tests for memory, critical flicker fusion and reaction times after operation in all groups compared with values before operation. However, there was no significant difference between the propofol and enflurane groups, and no difference in recovery times. Enflurane anaesthesia without hypotension caused deterioration in psychometric tests similar to that in the study groups, except for a significantly smaller increase in reaction times after operation. The shorter duration of operation in the control group may explain this difference.

We have failed to show any measurable cerebral protection from propofol compared with enflurane anaesthesia during prolonged hypotensive anaesthesia. We also failed to show any deleterious effects of hypotensive anaesthesia on higher cerebral function. Both study groups provided satisfactory operating conditions, but propofol was less effective than enflurane in inducing hypotension.

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British Journal of Anaesthesia 1993; 71: 898–901

CASE REPORTS

COMPLICATIONS OF TRACHEOTOMY

M. D. MANSFIELD, G. C. PUGH AND M. BROCKWAY

SUMMARY

A patient underwent elective tracheotomy before resection of the floor of the mouth. After operation, several life-threatening complications arose from this tracheotomy, including surgical emphysema of the tracheal mucosa which has not been described previously. (Br. J. Anaesth. 1993; **71**: 898–901)

KEY WORDS

Complications: tracheal mucosa surgical emphysema. Surgery: tracheostomy.

CASE REPORT

A 54-yr-old man weighing 69 kg presented with a moderately differentiated squamous cell carcinoma of the floor of mouth. The tumour was unsuitable for treatment by radiotherapy and urgent resection was therefore indicated. Past medical history included a perforated peptic ulcer (1959), partial gastrectomy (1961) and right basal pneumonia (1981). He smoked 20 cigarettes per day, had a moderate alcohol consumption (15 units per week) and was not receiving any medication.

Preoperative examination revealed a palpable, tender left submandibular gland and an ulcerated lesion on the left floor of mouth extending over the alveolar ridge. Physical examination and preoperative investigations, including full blood count, urea and electrolyte concentrations, liver function tests, ECG and chest X-ray, were unremarkable.

The patient was premedicated with oral diazepam 10 mg 1 h before operation. Anaesthesia was induced with thiopentone and intubation of the trachea (cuffed Portex 9.0-mm tracheal tube) facilitated with suxamethonium. Anaesthesia was maintained with halothane and 66 % nitrous oxide in oxygen. Neuromuscular block was produced with atracurium and analgesia with papaveretum. To assist surgery, hypotension was induced using an infusion of sodium nitroprusside combined with trimetaphan, titrated to maintain systolic arterial pressure at approximately 90 mm Hg.

Tracheotomy was performed before resection of the tumour to facilitate surgical access and to secure the airway after operation because of the expectation of oedema of the remaining tongue and oral tissues. The skin incision was made vertically from below the cricoid cartilage to just above the supra-sternal notch. A circle of trachea was excised at the level of the fourth cartilaginous ring below the thyroid isthmus. A cuffed armoured Lar-a-ject tracheostomy tube (Sheridan, 7.0 mm) was then inserted and the tracheal tube withdrawn. Intermittent positive pressure ventilation (IPPV) was continued through the tracheotomy.

Surgery was performed through a collar incision, 6 cm above the tracheostomy site. After bilateral suprahyoid dissection and clearance, the tumour was excised with the mucosa over the alveolus and a 3-cm segment of mandible on the left side. Through a paramedian abdominal incision, a segment of jejunum was excised with its vascular pedicle. The opened jejunum was used to close the defect in the mouth and its vascular supply restored by anastomosis to the left internal jugular vein and left external carotid artery.

On completion of surgery, residual neuromuscular block was antagonized. The Lar-a-ject tube was removed and replaced with a cuffed Portex 8.0-mm tracheal tube secured by two tapes around the neck. After an uneventful recovery, the patient was returned to the ward, breathing spontaneously through a humidified T-piece system (inspired oxygen concentration ($F\text{I}_{\text{O}_2}$) = 0.4; arterial oxygen saturation ($S\text{p}_{\text{O}_2}$) = 95 %) (Ohmeda Biox 3700 pulse oximeter). He was nursed by staff experienced in the postoperative management of patients with a tracheostomy.

At 10:00 on the second day after operation the patient developed acute upper airway obstruction associated with hypoxia and cyanosis. He became acutely distressed and was noted to be breathing through the mouth with difficulty. The tracheostomy tube was found to be lying outside the trachea in the subcutaneous tissues of the neck. Efforts by medical staff to reinsert the tube into the trachea failed, and attempts at IPPV led to extensive surgical emphysema of the chest wall and mediastinum. The patient aspirated blood-stained fluid during this period. It was considered safest to transfer him to theatre for urgent revision of the tracheostomy. Anaesthesia was induced and maintained with isoflurane in oxygen. In theatre it was clear that the tracheostomy tube was situated in a false passage outside the trachea. The thyroid isthmus was seen to

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be overlying the tracheostomy and was therefore divided. The tracheal orifice was enlarged superiorly and, for ease of fit, a Portex 7.5-mm tracheal tube inserted, which was then secured by sutures to the skin.

On his return to the ward, breathing through an identical T-piece system, the patient's gas exchange had deteriorated such that, with $F\text{I}_{\text{O}_2} = 0.8$, the $S\text{p}_{\text{O}_2}$ was 80%. Chest x-ray showed extensive surgical emphysema of the chest wall and mediastinum and bilateral middle and lower zone patchy opacification of the lungs consistent with aspiration. Although the upper airway was clear and the tracheostomy tube was in the correct position, there was reduced air entry to both lungs. Subsequently, $S\text{p}_{\text{O}_2}$ decreased to 40% ($F\text{I}_{\text{O}_2} = 0.8$) and increased to only 70–80% with IPPV ($F\text{I}_{\text{O}_2} = 1.0$). Another chest x-ray showed increased bilateral opacification throughout both lung fields consistent with adult respiratory distress syndrome (ARDS). The patient was therefore transferred to the hospital's high dependency unit (HDU) for continued ventilation of the lungs.

High frequency jet ventilation (HFJV) was commenced proximally through the tracheostomy ($F\text{I}_{\text{O}_2} = 0.8$, driving pressure (DP) = 1.7 bar, frequency (f) = 150 b.p.m.; inspiratory time (IT) = 0.3 s) (Acutronics jet ventilator AMS 1000), in addition to spontaneous ventilation via a T-piece ($F\text{I}_{\text{O}_2} = 0.8$). This combination resulted in $S\text{p}_{\text{O}_2}$ 95–97%. Chest x-ray appearances were unchanged at this time.

The patient's condition remained stable overnight, but at 06:00 on the third day after operation he developed acute respiratory distress, with $S\text{p}_{\text{O}_2}$ 82% and hypotension. On examination there was no obvious pneumothorax. He was breathing through his mouth, albeit in an obstructed manner, but not through the tracheal tube (the tracheostomy tube cuff was still inflated, although obviously not providing a tracheal seal). HFJV was ineffective. Fibreoptic bronchoscopy (Olympus, diameter 4.0 mm), performed through the tracheostomy tube, revealed a grossly abnormal trachea. There was marked ballooning of the mucosa (pink in colour) causing virtually complete obstruction of the tracheal lumen. The appearance was not like oedema, but resembled several "envelopes" of tissue extending to the carina (the carina itself and main bronchi distal to it were of normal appearance). It was presumed that these lesions were obstructing the distal orifice of the tracheostomy tube, whilst only partially obstructing the trachea itself, allowing the patient to breathe through his mouth. The envelopes of tissue were displaced easily by the tip of the fibreoptic bronchoscope. A suction catheter (14-French gauge) was then passed through the tracheostomy tube, past the obstructed area of trachea, into the right main bronchus under fibreoptic guidance. HFJV was then restarted ($F\text{I}_{\text{O}_2} = 0.7$, DP = 1.7 bar, f = 150 b.p.m., IT = 0.3 s) through the catheter with immediate improvement in oxygen saturation ($S\text{p}_{\text{O}_2}$ 95%). Fibreoptic bronchoscopy at this time showed resolution of the tracheal lesions, which prompted the conclusion that surgical emphysema of the tracheal mucosa had occurred. The Portex tracheostomy tube was then removed and a Hi-Lo jet tracheal tube (Mallinckrodt, 7.0 mm) was passed over the suction catheter to lie just above the carina. The suction catheter was then removed and HFJV continued successfully through the Hi-Lo tube. After stabilization of the patient's condition, a chest x-ray revealed a left-sided pneumothorax and an intercostal drain was inserted.

Sixteen hours later, another acute deterioration in ventilatory status occurred. Chest x-ray showed a moderate sized, right-sided pneumothorax and another intercostal drain was inserted. Fibreoptic bronchoscopy at this time showed marked oedema, with some ulceration of the tracheal mucosa extending down to the carina. Again, the carina and the distal main bronchi appeared relatively normal.

In view of the patient's deteriorating condition, and because of suspected tracheal laceration and possible rupture, he was transferred to the cardiothoracic intensive care unit (ICU) at a nearby hospital. At the time of transfer he was awake and co-operative, breathing spontaneously through the Hi-Lo jet tube with HFJV superimposed ($F\text{I}_{\text{O}_2} = 0.8$; $S\text{p}_{\text{O}_2} = 96\%$).

For the next 4 days, HFJV was continued with overall improvement culminating in a 24-h period of unassisted spontaneous ventilation. However, the patient tired, his arterial blood-gas tensions deteriorated and HFJV was restarted. He began to produce increasing amounts of purulent sputum, from which *Pseudomonas* was isolated. Subsequently, he developed bilateral bronchopleural fistulae and empyemata, and the tracheostomy tube eroded the surrounding tissues, resulting in the formation of a tracheo–oesophageal fistula. The tracheostomy site became infected and enlarged, which made fixation of the tube difficult, necessitating replacement on several occasions. In an attempt to treat his worsening respiratory function IPPV was commenced (Servo 900C ventilator, volume control).

From day 10, the patient developed progressive circulatory and then renal failure. He received inotropic support, but developed multi-system failure and died 34 days after operation. Postmortem examination was not performed, but histological examination of the surgical specimen showed that the tumour extended to the resection margin.

DISCUSSION

This case report serves first to remind of the dangers associated with tracheotomy and, second, describes a previously unreported and life-threatening complication.

The problems encountered in this patient may be attributed in part to the original tracheotomy procedure. A low position was chosen deliberately to facilitate surgical access. Tracheotomies are usually performed with the neck extended, but when combined with a low position there is an increased likelihood of the tracheal orifice being located in the thoracic portion of the trachea. When the head and neck are returned to the neutral position, this creates a longer track from skin to trachea, making tracheostomy tube placement more difficult. Furthermore, low tracheostomies are associated with an increased incidence of surgical emphysema of the mediastinum [1], because more extensive dissection may be required. Also, the "standard" tracheotomy (i.e. resecting a circle of trachea) is associated with more tracheostomy tube re-insertion problems than other techniques, such as the Bjork flap [1]. These potential problems were experienced subsequently when the tracheostomy tube became displaced.

Prevention of the extubation would have been the optimal management for this patient; however, it occurred during an intense coughing episode, despite fixation that had previously appeared satisfactory, and we can suggest nothing that would have guaranteed against it. The use of tapes to secure a tracheostomy tube is widespread and usually very effective; it was our method of choice for fixation and we had experienced no major problems with them before this case. We decided to suture the second tracheostomy tube in position on the basis that, in this patient, the tapes had proved ineffective, and in the hope that suturing would offer more security (although aware that suturing makes replacement more difficult should extubation occur); there was no further accidental extubation.

The tube proved impossible to replace on the ward. Important factors causing this were the generalized swelling of the tissues after operation and the fact that the thyroid isthmus overlay the tracheostomy. It was fortunate that the patient could breathe to a certain extent through his "conventional" airway and this allowed us time to transfer him to theatre. If he had been unable to do this, immediate oro- or nasotracheal intubation would have been indicated, although he was an obvious candidate for difficult intubation because considerable post-operative intra-oral/pharyngeal swelling would be expected. The patient was understandably distressed in theatre and we embarked on a gaseous induction on the grounds that his airway was likely to prove difficult; however, when he was anaesthetized his airway actually improved and was relatively easy to maintain with a face mask whilst the tracheostomy was refashioned. Laryngoscopy was not performed because of the jejunal graft.

The decision to replace a tracheostomy tube that had become displaced with one identical in length might be questioned, especially when the tracheostomy tract was known to be long. It could be argued that a longer tube (which we did use subsequently) may have been indicated. However, the tracheostomy had been extended superiorly, thus shortening the tract, and there were no further security problems. Nevertheless, in retrospect, it is possible to envisage that the tips of the tracheostomy tubes interfered with the lower margins of the tracheostomy incision. If this were the case, a significant role in the initiation of subsequent events (i.e. tracheal emphysema, pneumothoraces and possible tracheal rupture) may be attributable to it. Earlier insertion of a longer tube may have restricted tracheal damage.

Airway obstruction, and the associated hypoxia at the time of tube displacement, may have provoked the vomiting that occurred in this patient. The aspiration pneumonitis that followed was responsible for the subsequent deterioration in respiratory function.

High frequency jet ventilation proved effective initially, providing adequate gas exchange. However, in the presence of a breach in the tracheal mucosa (which is normally firmly adherent to the tracheal wall), this ventilation technique presumably produced the surgical emphysema. As HFJV was being performed proximally, within a T-piece arrangement, the tracheal mucosa was not exposed directly to the driving pressure. This suggests that surgical emphysema of the trachea could possibly occur with conventional IPPV also. The rapid resolution of the condition after the site was bypassed with the suction catheter, implies that it must have been air in the tracheal submucosa which was responsible. Although surgical emphysema in tissues typically does not resolve rapidly, air under the tracheal mucosa may behave differently and disappear quickly.

This life-threatening complication is previously undescribed, which is not surprising for several reasons: first, the rapid resolution may cause it to be undemonstrable at postmortem examination; second, fibreoptic techniques have become readily available only recently; third, the combination of a traumatic tracheotomy and HFJV is relatively uncommon, and therefore complications, if dependent on both, will be rare.

At the time of the initial fibreoptic examination we were unsure of the diagnosis, but bypass of the lesion was required urgently. The technique of passing a catheter into the bronchus and using HFJV through it is well described [2–4], and could be used irrespective of the nature of the tracheal lesion causing obstruction, provided that there is an expiratory pathway. It is noteworthy that the emphysema had not completely obstructed the trachea, allowing the patient to breathe through his mouth. It is implicit that the cuff of the tracheostomy tube was not sealing the trachea, possibly because of his respiratory efforts, or perhaps because the cuff was no longer in the trachea (at the time it was not possible to view the depths of the tracheostomy).

The pneumothoraces that occurred were not unexpected in view of the patient's extensive mediastinal surgical emphysema, the presumed mechanism being accumulation of air leading to external rupture of the pleura [5]. At the time when he developed respiratory distress from the tracheal emphysema, we initially considered the presence of pneumothorax, but clinical examination failed to confirm this. When stability had been achieved, pneumothorax was revealed on chest x-ray. It is possible that this pneumothorax was present when tracheal obstruction was diagnosed, although the fact that the patient's condition stabilized rapidly despite its presence indicates that it was not primarily responsible for his distress. It is also conceivable that, if complete obstruction of the trachea occurred at any stage when proximal HFJV was being performed, an associated increase in proximal airway pressure could have produced a pneumothorax. However, with the HFJV–T-piece arrangement, the proximal airway is always open to atmosphere (or a PEEP valve) and thus any pressure increases are minimized. Indeed, recordings of peak inspiratory pressure failed to demonstrate any untoward changes.

We still consider that HFJV is a useful aid in selected patients and feel that most of the problems encountered by this patient were directly attributable to the tracheotomy rather than the ventilatory technique. Although a contribution from HFJV cannot be excluded, we have had no further cause for concern in similar and other types of patients in whom HFJV has been used.

The final complication directly attributable to the tracheotomy in this patient was the tracheo-oesophageal fistula; the repeated trauma of surgery (probably resulting in a tear of the tracheal mucosa), several tube replacements, tracheal mucosal stripping, ulceration of the tracheal wall, and the infection around the tracheostomy may all be implicated in its formation.

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COMPARTMENT SYNDROME AFTER USE OF AN AUTOMATIC ARTERIAL PRESSURE MONITORING DEVICE

P. VIDAL, P. J. SYKES, M. O'SHAUGHNESSY AND K. CRADDOCK

SUMMARY

A case of compartment syndrome is reported as a rare complication of the use of a continuous arterial pressure monitoring device. For surgical procedures of very long duration, the way in which these monitoring devices are used may need to be modified, or alternative forms of pressure monitoring used. (Br. J. Anaesth. 1993; **71**: 902–904)

KEY WORDS

Complications: compartment syndrome. Monitoring: arterial pressure.

Compartment syndrome represents a group of symptoms and signs occurring together as a result of circulatory disturbance of the muscles and nerves in closed osseofacial compartments because of an increase in interstitial fluid pressure within those compartments. The only treatment for compartment syndrome is immediate and adequate surgical decompression of the compartments involved [1]. Failure to do so results in necrosis of muscle and gross impairment of nerve function and leads to Volkman's ischaemic contracture [2].

Many causes of compartment syndrome have been described, including the use of a pneumatic tourniquet [2]. We report a case of compartment syndrome resulting from the use of an automatic arterial pressure monitoring cuff.

CASE REPORT

A 21-yr-old man underwent reconstruction of his dominant right thumb under general anaesthesia using a left second toe microsurgical transfer. A crushing injury 11 months previously had resulted in loss of the thumb at metacarpal base level.

The patient's arterial pressure was monitored using an automatic Dinamap monitor which was applied to his left arm. The complete procedure from induction of anaesthesia lasted 8 h 10 min. This was longer than usual because of technical difficulties during the microsurgical transfer.

Immediately after recovery from the general anaesthesia, the patient complained of pain in the left arm. Examination of the area showed erythema and a distinctive pattern of grazes which corresponded to the shape of the pressure cuff (fig. 1). On further examination, 2 h later, the patient complained of increasing pain and dysaesthaesia in the fingers in the distribution of both the median and ulnar nerves. On palpation, the arm was tender and tense and flexion and extension of the elbow produced pain in the extensor and flexor aspects of the arm, respectively. There was a 4-cm difference in the girth of the arms (left greater than right).

Compartment pressures were measured with an arterial pressure measuring transducer and found to be consistently greater than 45 mm Hg. A diagnosis was made of compartment syndrome involving the flexor and extensor compartments of the arm. The patient was returned to the operating theatre 4.5 h after the earlier surgery had been completed and, under general anaesthesia, underwent a decompression fasciotomy of the flexor and extensor compartments of the affected arm. The subcutaneous tissue was found to be very oedematous and the muscles were very tense beneath the fascia and bulged markedly following release from the fascial compartments (figs 2, 3). However, all muscles were viable. After operation the patient's symptoms were completely relieved. The skin incisions were closed primarily 4 days later and the patient has since remained symptom-free.

DISCUSSION

The automatic Dinamap monitor initially inflates to a pressure which is greater than the normal adult systolic arterial pressure (about 180 mm Hg) and deflates by 8 mm Hg every 2 s until a pulsed pressure wave is detected. The pressure at which the pulsed pressure wave is detected corresponds to the patient's arterial pressure and is memorized by the Dinamap; subsequent cuff inflations are then automatically set so that the cuff pressure just exceeds the previous arterial pressure measurement. Cuff inflation was set in our patient to occur very frequently initially and then at 5-min intervals when the patient's arterial pressure had stabilized. The inflation time was less than 40 s.

In this particular patient, the arterial pressure was both labile and high. This situation produced a longer than usual scanning time at a greater than normal pressure. During the course of the microsurgical procedure, arterial pressure recordings were made a total of 805 times!

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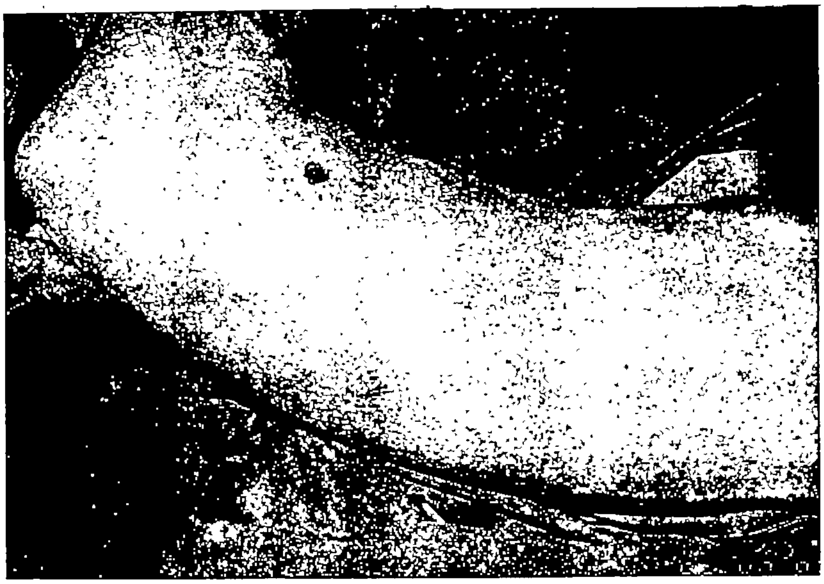

FIG. 1. Skin marks produced by the pressure cuff.

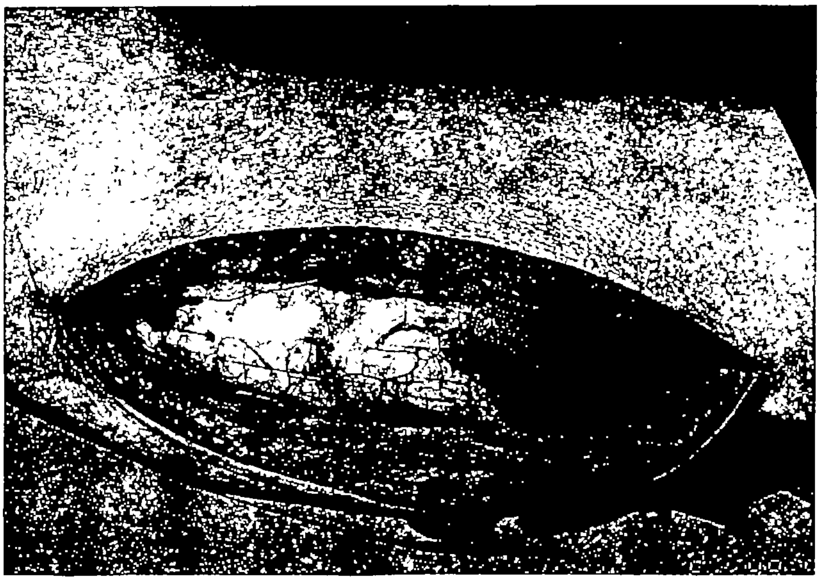

FIG. 2. Extensor compartment immediately after decompression.

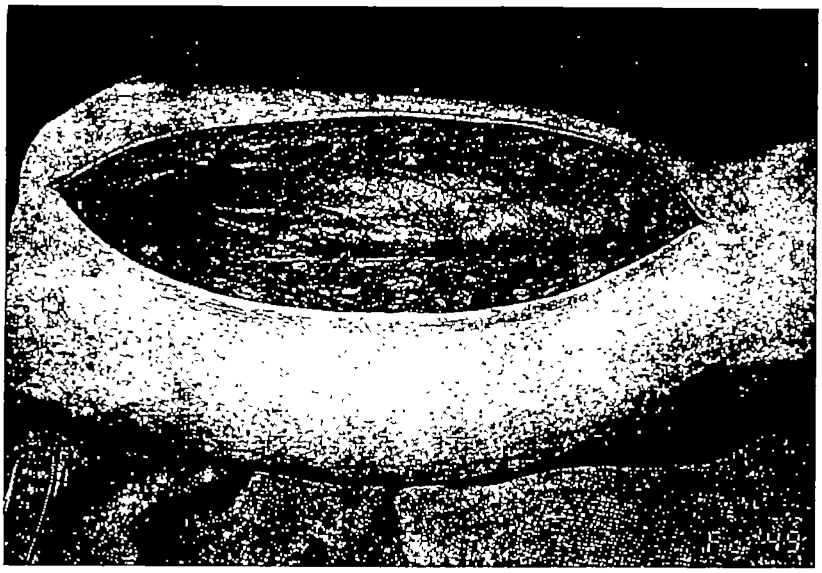

FIG. 3. Flexor compartment immediately after decompression.

Median, ulnar and radial nerve neuropathies have been described after the use of automatic arterial pressure measuring machines during the course of surgical procedures lasting between 1 and 6 h. None of the patients reported, however, demonstrated symptoms and signs consistent with an actual compartment syndrome [3], and all resolved spontaneously within days without the need for decompression fasciotomy [4–8].

The automatic Dinamap arterial pressure monitor has an excellent record of safety in clinical practice [9]. For prolonged monitoring, however—as in many microsurgical procedures—the way in which this machine is used may need to be modified, for example by reducing the frequency of readings. Alternatively, the use of arterial cannulation to measure the patient's arterial pressure may appear more prudent.

We report this case to make both surgeons and anaesthetists aware of the risk of the unusual, but potentially very serious, complication of compartment syndrome after the prolonged use of an automatic arterial pressure monitoring device.

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EQUIPMENT

TRACHEAL INTUBATION IN A MANNIKIN: COMPARISON OF THE BELSCOPE WITH THE MACINTOSH LARYNGOSCOPE

U. M. HODGES, D. O'FLAHERTY AND A. P. ADAMS

SUMMARY

Tracheal intubation carries a risk of accidental oesophageal intubation; this is increased with inexperienced trainees, and in patients with a difficult airway. The recent introduction of an angulated laryngoscope, the Belscope, may permit a better view of the vocal cords and increase the accuracy of orotracheal intubation. To determine how easy it is to learn to use the Belscope compared with the traditional Macintosh laryngoscope, a group of medical students attempted to intubate a mannikin which had been modified to simulate a difficult intubation. Time to intubation was fast with both laryngoscopes, although faster with the Macintosh, but the Belscope produced an unexpected greater incidence of failed intubation. (Br. J. Anaesth. 1993; **71**: 905–907)

KEY WORDS

Intubation, tracheal: training. Equipment: laryngoscope.

The Belscope laryngoscope (fig. 1) may be used for both routine and difficult tracheal intubation [1]. It has an angulated blade which provides a better view of the larynx than the Macintosh laryngoscope when optimal placement of the laryngoscope blade is restricted by limited atlanto-occipital extension, by a large tongue or a short mandible. It has been suggested that this laryngoscope should be readily available for practice and training purposes for anaesthetists [2]. In our department, we participate in the training of resuscitation skills and are therefore involved in providing practice and training for non-anaesthetists. We teach intubation skills to medical students on their anaesthetic attachment initially with mannikins and then in selected patients, and have noticed both oesophageal intubation and a failure to recognize this complication when it occurs [3]. Any technique which would decrease the incidence of failed intubation, particularly when laryngoscopy is not grade 1 according to the Cormack and Lehane classification [4], would be valuable.

The Belscope has been used regularly in clinical practice for more than 3500 tracheal intubations [1], but no formal assessment has been reported. The purpose of this study was to ascertain if the Belscope laryngoscope is easier for medical students to use than the "conventional" Macintosh laryngoscope.

METHODS

Twenty-five medical students who had not yet started their anaesthetic training were invited to pass a tracheal tube into a mannikin (Laerdal airway management trainer) which had been adjusted (by one of the authors) so that only the posterior extremity of the glottis was visible using a Macintosh blade—this corresponds to grade 2 of Cormack and Lehane's classification [4]. In this type of mannikin, mouth opening is greater than 2.5 cm and the "intubation" angle > 95°. An intubation angle of less than 95° reflects severe limitations of head extension on the neck [5] and both this and restricted mouth opening are possible causes of failure to intubate with the Belscope [1]. The medical students were asked to intubate the trachea using the Macintosh laryngoscope with the size 4 blade or the long-bladed Belscope laryngoscope.

A standard description and demonstration of both methods was given to each student. This was followed by a short practice at the grade 1 level of difficulty for up to 15 min until the student intubated successfully with both laryngoscopes. Each student then attempted tracheal intubation at the preset grade 2 level of difficulty—maximum 60 s allowed—20 times in succession, using the two types of laryngoscope alternately. The time from the blade

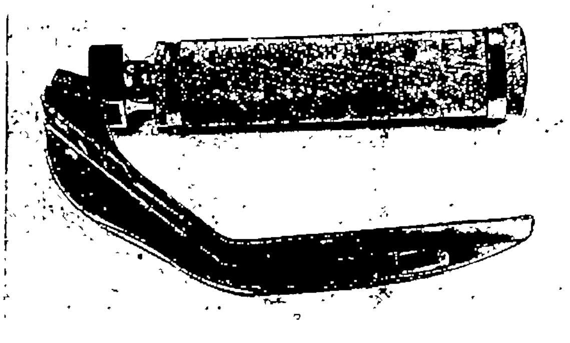

FIG. 1. The Belscope laryngoscope.

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passing the lips of the mannikin to the successful placement of the tube was recorded in each case. Tracheal intubation was confirmed by inflating the lungs of the mannikin after each attempt was completed; the student was not blinded to the result. For each successful intubation the student was asked to assess the level of difficulty, using a visual analogue scale (VAS) from 1 = extremely easy, to 100 = impossible. The number of failed intubations, defined as requiring more than 60 s or resulting in oesophageal intubation, was recorded.

Results were analysed using Wilcoxon's rank sum test for non-parametric data (Minitab Statistical Package release 8 [6]).

TABLE I. *Number of failed intubations and median (interquartile range) number of failed intubations per student, time to intubate and degree of difficulty.* † *Each student made 10 attempts to intubate with each laryngoscope*

	Macintosh	Belscope	*P*
No. intubations	230	230	
Number failed	12	50	
Failures per student†	0 (0–1)	2 (1–3)	0.002
Time to intubate (s)	13 (10–16)	17 (12–23)	0.003
Degree of difficulty (VAS 0–100 mm)	22 (14–36)	32 (20–52)	0.006

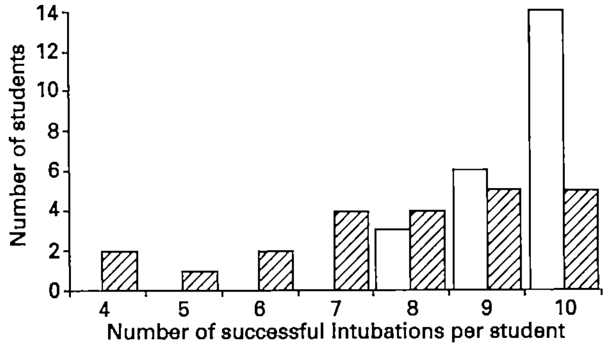

FIG. 2. Number of successful intubations from 10 attempts per student. $P = 0.002$ between Macintosh (□) and Belscope (▨) laryngoscopes.

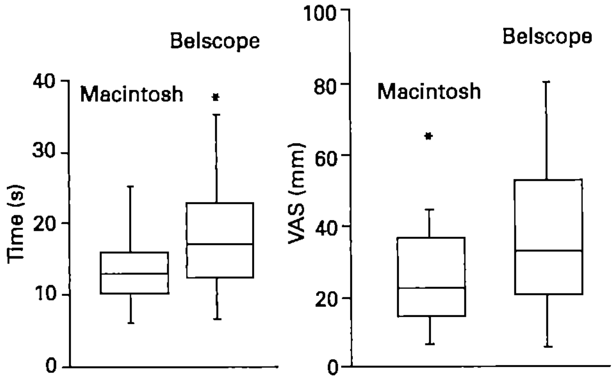

FIG. 3. A: Percentile box plot of time (s) to intubate. B: Percentile box plot of visual analogue scores (VAS). The box shows the difference between the quantiles, with the median marked as a line and bars show the extremes. The asterisk shows a possible outlier [6]. Significant differences between Macintosh and Belscope laryngoscopes: $P = 0.003$ for time to intubate and $P = 0.006$ for VAS.

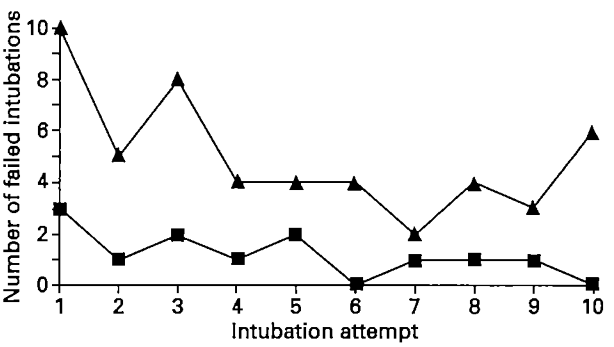

FIG. 4. Change in number of failed intubations with practice using the Macintosh (■) and Belscope (▲) laryngoscopes. The difference between the first five and second five attempts was significant for both ($P < 0.01$).

RESULTS

Two of 25 students failed, within the original 15 min allowed, to intubate successfully a grade 1 laryngoscopy and were excluded from the rest of the study.

The results from the remaining 23 students are shown in table 1. A total of 460 intubations were attempted. The Belscope laryngoscope produced significantly more failed intubations (50/230) (table I); 54% of these were unrecognized oesophageal intubation, and in 46% the student exceeded the time permitted. With the Macintosh laryngoscope there were 12/230 failures: 67% were unrecognized oesophageal intubation. The median difference in overall failure per student is 2 (fig. 2) (95% confidence interval (CI) 1–3) ($P = 0.002$). The time to successful intubation was longer with the Belscope laryngoscope (fig. 3A). The median difference was 4 s (95% CI 2–7 s) ($P = 0.003$). The degree of difficulty (VAS) with the Belscope was also significantly greater (fig. 3B): the median difference was 8 mm (95% CI 2–16 mm) ($P = 0.006$). Improvement with practice was observed (fig. 4), with the difference in the number of failed intubations between the first five and the second five attempts being significant for both methods ($P < 0.01$).

DISCUSSION

The Macintosh laryngoscope elevates the epiglottis indirectly by stretching the hyo-epiglottic ligament [7]. Sometimes the hyoid bone cannot be adequately displaced forward and the epiglottis continues to obstruct the view of the larynx. The Belscope lifts the epiglottis directly [1] and the back of the tongue is flattened. It facilitates direct laryngoscopy when optimal placement of the laryngoscope blade is restricted by limited atlanto-occipital extension, a large tongue or a short mandible, so it has been used in grade 3 or more difficult laryngoscopies. The "learning curve" is said to be easy [2] and it is recommended for routine laryngoscopies [1].

It is important that all doctors (and medical students) should achieve competence in cardiopulmonary resuscitation, and therefore intubation [3, 8]. In a previous study [9] of the cardiopulmonary resuscitation skills of pre-registration house officers, 45% of the doctors tested failed to intubate a mannikin and those that were successful took longer than 35 s (upper limit of time allowed for pass grade in advanced Cardiac Life Support examination in the United States) [10]. The Macintosh laryngoscope is widely recommended at present to non-anaesthetists [8, 11, 12]. As we have found previously that failed intubation by students is related to the degree of difficulty at laryngoscopy [3], the Belscope blade (which is designed to facilitate otherwise difficult intubation) might reduce the observed incidence of failed intubations. As grade 3 laryngoscopy is found only in about 1.7–3% of patients [13, 14], it seemed appropriate to use the grade 2 difficulty of laryngoscopy as the test. The students received our standard training in intubation as described previously [3]. The two who failed to intubate a grade 1 laryngoscopy within the 15 min allowed were excluded. The remaining 23 students, after demonstrating that they could intubate a grade 1 laryngoscopy, entered the study and with both types of laryngoscope learned to intubate a grade 2 laryngoscopy.

The designer of the Belscope has suggested that it should be contraindicated for use in rapid sequence induction because "the Macintosh blade has been found marginally quicker to use" [1]. In our study, although the time to intubation was faster with the Macintosh laryngoscope, both laryngoscopes met the criteria for time to intubation laid down by the American Advanced Cardiac Life Support examination. The times to intubation compared well with the results reported by experienced anaesthetists using other instruments [15]. The visual analogue scores were not high with either blade, although the Macintosh had better scores.

The major unexpected difference between the two blades was in the number of failed intubations, although the students did better with both laryngoscopes than the house officers reported previously [9]. Of the 230 intubation attempts made with each laryngoscope, there was a 5% failure rate overall with the Macintosh laryngoscope and a 21% failure rate with the Belscope. For both laryngoscopes, the majority of the failures occurred within the first five attempts (75% for the Macintosh and 62% for the Belscope) and the majority of failures were oesophageal intubation. The students considered two factors to be important with the Belscope. First, they found that when the Belscope blade had been placed correctly it tended to slip out of position more readily than the Macintosh blade. This may be related to the nature of the plastic "tissues" of the mannikin rather than to the blade itself, but it is difficult to see why a similar effect was not seen with the Macintosh. Second, they found it difficult to see the larynx clearly when the tracheal tube was inserted into the mouth. This might be overcome by the use of an introducer in the tube [2].

In conclusion, we were impressed by the students' speed of intubation and low failure rate with the Macintosh laryngoscope. Failed intubation was more likely using the Belscope and we cannot recommend it as a replacement for the Macintosh laryngoscope for routine laryngoscopy by non-anaesthetists.

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British Journal of Anaesthesia 1993; 71: 908–914

COMMENTARIES

PLASMA DRUG CONCENTRATIONS: DESCRIPTION AND INTERPRETATION OF THE BIEXPONENTIAL DECAY

V. NIGROVIC

SUMMARY

Information about the time course of the plasma concentrations of a drug after its i.v. bolus injection is necessary for understanding the time course of the effect of the drug. If an investigator has established that the time course of the plasma concentrations conforms to a biexponential function, understanding the data is facilitated by description *of the time course which simply summarizes the data in a quantitative fashion and* interpretation *of the findings based on certain assumptions. Interpretation may be based on the assumption of compartments, or on a "whole body" approach. The experimentally obtained plasma concentrations of a drug may be described quantitatively by an equation and, if the "whole body" interpretation is selected in preference to the compartmental interpretation, the four parameters are: the initial and the terminal volumes of distribution (V_C and V^{term}) and the rate constants for the loss from V_C and for the dilution within the whole body (k_{loss} and k_{mix} respectively).* (Br. J. Anaesth. 1993; **71**: 908–914)

KEY WORDS

Pharmacokinetics: models.

Information about the time course of the plasma concentration of a drug after its i.v. bolus injection is necessary for understanding the time course of the effect of the drug. It is no surprise, then, that this information has been made available for the majority of drugs introduced into clinical use during the past 2 decades. Incorporation of this information into clinical practice is, however, difficult for two reasons: first, the description of the time profile of the plasma concentrations is frequently reported incompletely and, even if the complete description is available, the information is not presented in a way that would be understood easily; second, a variety of additional pharmacokinetic terms is included without an appropriate definition of their relationship to the experimental data.

The objective of this paper is to facilitate understanding of the reported data. Given the fact that the investigator has established that the time course of the plasma concentration conforms to a biexponential function, the task is subdivided into *description* of the time course and *interpretation* of the findings. It is necessary to separate these two clearly: the first simply summarizes the data in a quantitative fashion; the second offers an explanation for the findings based on certain assumptions. One interpretation is based on the assumption of compartments; it is dealt with thoroughly in textbooks [1–4] and will be discussed only briefly. The other interpretation is based on a different set of assumptions and will be explored here. Both are equally suitable to interpret the biexponential decay of the plasma concentrations of a drug; the selection of one or the other method of interpretation depends on the needs of the investigator.

BIEXPONENTIAL DECAY

Quantitative description

The standard way of presenting a biexponential decay for the plasma concentrations of a drug is:

$$C = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} \qquad (1)$$

where C = plasma concentration at any time after the injection; A and B = extrapolated (to time $t = 0$ min) concentrations in plasma; concentrations disappear from plasma with the hybrid (or macro) rate constants α and β (in units of reciprocal time), respectively; e = base of the natural logarithms. By definition, $\alpha > \beta$. It has become customary to report also the rate constant β in terms of half-life ($T_{\frac{1}{2}}$ in units of time); half-life represents a simple conversion of any rate constant:

$$\text{half life} = \ln(2)/\text{rate constant}$$

Reporting the biexponential decay of the plasma concentration of a drug in this form is not optimal. First, the drug is not identified as such and it is not directly obvious that the symbols refer to concentrations, specifically in plasma. Other disadvantages are more important: the role of the injected dose is not evident and the coefficients A and B change with the dose. Finally, it is difficult to "read" this equation.

The presentation may be formally changed. The notation:

$$V_C = \frac{Dose}{A+B} \qquad (2)$$

brings the injected dose explicitly into the equation and introduces an important new variable, V_C—that

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volume of a space into which the dose of the drug would be diluted were a uniform concentration in plasma achieved instantaneously at the moment of the bolus injection. The substitution allows replacement of the dose-dependent coefficients A and B by a single dose-independent coefficient. After division by $(A+B)$, the first coefficient, A, becomes the new coefficient M, and B becomes $(1-M)$. If the concentration in any space is denoted by square brackets subscripted by the name of the space, then the plasma concentration of a drug Z at any time t is given by:

$$[Z]_P{}^t = \frac{Dose_z}{V_C}(M\cdot e^{-\alpha\cdot t}+(1-M)\cdot e^{-\beta\cdot t}) \qquad (3)$$

M denotes the fraction of the dose that decays with the rate constant α. This equation may now be read as follows: with any dose, the fraction M decays rapidly. The larger the value of M the larger the fraction of the dose that decays rapidly. Consequently, a smaller fraction remains to disappear from plasma with the slower rate constant, β. It is evident that an increase in *Dose* results in proportionately greater plasma concentrations. Also, the equation specifies that the dose is initially diluted in a space of an apparent volume, V_C, that is explicitly stated. The value of M must lie between 0 and 1 for a biexponential decay. If M is assumed to be equal to 1 or to zero, the biexponential function is converted into a monoexponential one. The "kinetic" part of the equation is contained within the parentheses. It provides an image of the time profile for the plasma concentrations of a drug. The image is independent of the administered dose or of V_C. Other advantages of this method of presentation will become evident later.

The four dose-independent parameters in equation (3) (V_C, M, α and β) provide a complete description for the biexponential decay of the plasma concentrations.

Why do the plasma concentrations of any drug decrease with time?

The *description* of the time course of the plasma concentrations does not provide an insight into the fate of the drug in the body. The same biexponential decay may be *interpreted* in different ways. However, any interpretation is based on the parameters supplied by the description. The number of parameters used in the interpretation is limited to the number of parameters provided by the description.

One way of answering the above question is to consider the body as a whole. This conceptual approach of interpreting the plasma concentrations deliberately neglects any detailed considerations, such as the fact that the body consists of various tissues and the drug may reach them at different rates and in different amounts. Necessarily then, this interpretation is a simplified representation of the processes that actually take place in the body.

The "whole body" interpretation depicts the decrease in plasma concentration of a drug as the result of two processes. The first is *loss* of the drug from the body. This may occur either by excretion from the body or by chemical alteration (metabolism) within the body. In both cases, the lost amount of the drug is no longer present in the body. The second process is *dilution* of the drug within the body. Dilution does not change the amount of the drug in the body, but only the concentration in plasma. Although both the loss and the dilution occur simultaneously starting at the moment of injection, they are considered first separately and, later, the interplay of both processes is discussed.

Loss of the drug from the body. Many processes that cause loss of a drug from the body occur at rates that are proportional to the amount of the drug in the body—that is, by a first-order process [5]. Such a process may be described, for example, by the statement that 10% of the drug is lost in 1 h. If 100 mg of a drug is present in the body at the start of the 1-h period, then at the end of 1 h 90 mg is present and 10 mg has been lost. If only 10 mg is present at the start, 9 mg remains and only 1 mg has been lost. The example shows that the amounts actually lost differ, but that the drug is lost at the same rate, namely at 10% per hour. The rate of loss is characterized by a rate constant that describes the fraction that is lost per unit time. In the following, the rate constant for loss is designated k_{loss} and, in the above example, k_{loss} is approximately 0.1 h^{-1}.

The majority of drugs are lost from the body by such a first-order process. All processes that contribute to the loss of the drug from the body are represented by a single rate constant for loss: its value is given by k_{loss}. When only the loss is considered, the whole body is represented as a single space, the volume of that space being designated V_{space}. It is assumed that a drug is injected into this space, a uniform concentration in it is reached instantaneously, and the drug is lost from throughout this space. The last condition stipulates that each molecule of the drug in the body has equal probability of being lost. Under these assumptions, the amount of the drug remaining in the body is expressed quantitatively by the exponential function:

$$\{Z\}_{wb}{}^t = \{Z\}_{wb}{}^{t=0}\cdot e^{-k_{loss}\cdot t} \qquad (4)$$

where the curly braces denote the amount of the drug Z; subscript wb = whole body; k_{loss} = rate constant for the loss; t = time. The rate constant k_{loss} is *the* variable that determines how fast the drug is lost from the body.

In medicine, it has become customary to describe the same fact in a different way. The thought process is as follows. At time $t = 0$ min, the total injected amount (= dose) is present in the body and is equal to the product of the plasma concentration at that time and V_{space}. At any time later, the amount remaining in the body is

$$\{Z\}_{wb}{}^t = (V_{space}\cdot[Z]_P{}^{t=0})\cdot e^{-k_{loss}\cdot t} \qquad (5)$$

The *rate of loss* of a drug from the body is obtained by differentiating the above equation [5]. It is equal to:

$$-\frac{d}{dt}\{Z\}_{wb} = (V_{space}\cdot[Z]_P{}^{t=0})\cdot(-k_{loss})\cdot e^{-k_{loss}\cdot t} \qquad (6)$$

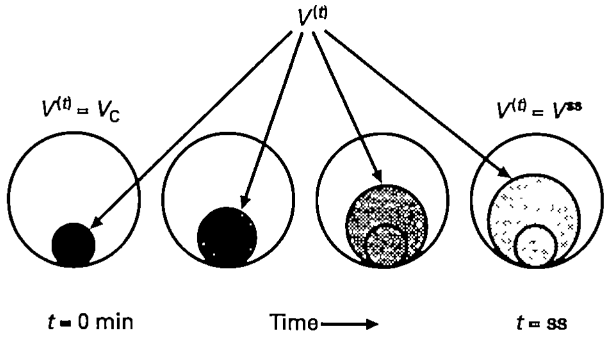

FIG. 1. *The concept of time-dependent volume of distribution, $V^{(t)}$.* The large circles represent the whole body. The injected dose of a drug is postulated to be diluted instantaneously in a space represented by the small circle ($t = 0$ min). The volume of this space is termed V_C, and represents the initial value of $V^{(t)}$. If the drug is not lost from the body, the total injected amount is progressively diluted into a space represented by the circles of increasing diameter. The decreased intensity of their shading indicates the decreasing concentrations in this space. The postulates that (i) the drug concentration in this space is uniform, (ii) the initial dilution space is contained within the increasing space of dilution and (iii) sampling occurs from the initial volume of dilution, allow calculation of the volume of the dilution space ($V^{(t)}$). After reaching steady state (t = ss) no further dilution occurs, and $V^{(t)}$ assumes the value V^{SS}.

The plasma concentration present simultaneously is given by:

$$[Z]_P{}^t = [Z]_P{}^{t-0} \cdot e^{-k_{loss} \cdot t} \qquad (7)$$

Dividing the rate of decrease of the amount of a drug in the whole body by the plasma concentration present simultaneously results in the following expression:

$$\frac{-\frac{d}{dt}\{Z\}_{wb}{}^t}{[Z]_P{}^t} = \frac{V_{space} \cdot (-k_{loss}) \cdot [Z]_P{}^{t-0} \cdot e^{-k_{loss} \cdot t}}{[Z]_P{}^{t-0} \cdot e^{-k_{loss} \cdot t}} \qquad (8)$$

The left-hand side of equation (8) is termed systemic (or whole body or plasma) clearance, Cl_{sys}. After simplification, equation (8) becomes:

$$Cl_{sys} = V_{space} \cdot k_{loss} \qquad (9)$$

In words, the systemic clearance represents the amount of a drug lost from the whole body per unit time. It is that volume of V_{space} that contains the drug in an amount equal to the amount lost per unit time. Assuming that V_{space} corresponds to the plasma volume, systemic clearance may be defined as follows: systemic clearance represents the volume of plasma that contains an amount of drug equal to that lost from the whole body per unit time. The systemic clearance does not change with time after the injection and is independent of the injected dose. These are the principal advantages of the concept of Cl_{sys}.

Dilution of the drug in the body. After injection of the drug, the amount administered is diluted progressively into a space that is larger than the initial dilution space (fig. 1). The initial volume of dilution, V_C, is postulated to be reached instantaneously. The progressive mixing leads to decreased plasma concentrations. If no loss of drug occurs, the amount in the whole body remains equal to the injected amount. The mixing process continues and the dilution space increases until the drug is diluted in all the space available to it, when dilution terminates. From this moment on, the plasma concentration remains constant. The constant plasma concentration indicates that no *net* movement of the drug occurs any longer and that *steady state* has been reached. If it is assumed that the concentration of the drug is uniform throughout this space and equal to the concentration in plasma, it is possible to calculate the volume of this space. It is called the volume of distribution at steady state, V^{SS}. As, for the time being, we consider that no loss occurs, the following equalities exist:

$$Dose_Z = \{Z\}_{wb} = V_C \cdot [Z]_P{}^{t-0} = V^{SS} \cdot [Z]_P{}^{SS} \qquad (10)$$

The process of dilution may be expressed quantitatively as follows. If dilution is the only process leading to the decrease in plasma concentrations of a drug, then the time course of the plasma concentrations is given by:

$$[Z]_P{}^t = ([Z]_P{}^{t-0} - [Z]_P{}^{SS}) \cdot e^{-k_{mix} \cdot t} + [Z]_P{}^{SS} \qquad (11)$$

The equation indicates that the plasma concentration decreases from the initial value at time $t = 0$ min, $[Z]_P{}^{t-0}$, to a constant value, $[Z]_P{}^{SS}$, with a rate constant for mixing, k_{mix}. It follows that $[Z]_P{}^{t-0} > [Z]_P{}^{SS}$. The plasma concentration at steady state results from mixing of the drug in a finite space. The volume of this space is denoted V^{SS}.

The continuous decrease of the plasma concentration from $[Z]_P{}^{t-0}$ to $[Z]_P{}^{SS}$ reflects the continuous increase of the space into which the drug is diluted. The time-dependent volume of this space is termed $V^{(t)}$. It increases from $V_C = V^{t-0}$ to V^{SS}. The rate of change of $V^{(t)}$ is dependent on k_{mix}. At any time t, $V^{(t)}$ is obtained by dividing the *amount* in the body by the concentration in plasma:

$$V^{(t)} = \frac{[Z]_P{}^{t-0} \cdot V_C}{[Z]_P{}^{SS} \cdot (1 - e^{-k_{mix} \cdot t}) + [Z]_P{}^{t-0} \cdot e^{-k_{mix} \cdot t}} \qquad (12)$$

From the above equation, it is evident that the volume of the space into which the drug is diluted increases with time: at time $t = 0$ min, it is equal to V_C and at a later time it eventually reaches V^{SS}. Therefore, $V^{SS} > V_C$.

The description of the process of dilution indicates two new variables: the rate of mixing or dilution, k_{mix}, and the time-dependent volume of dilution, $V^{(t)}$. Although the processes described are conceptually simple and plausible, their highly artificial nature must be emphasized. The rate of dilution may be interpreted as being dependent on the blood flow through the body and the chemical nature of the drug. Assuming that the rates for mixing are comparable between drugs, more time will be required to complete the mixing the larger the space available for mixing. More caveats must be applied when considering the volume term, $V^{(t)}$, and its two explicit values, V_C and V^{SS}. First, $V^{(t)}$ is, by definition, coupled to the concentration of the drug in plasma. It is not an independently measured estimate for the volume of the space into which the drug is diluted. Rather, it represents a dilution factor (in units of volume) that relates the amount of a drug in the whole body to the plasma concentration at the same time. The underlying assumption is that the total amount of a drug in the body is diluted to a uniform concentration, and the concentration is equal to that in plasma. Thus $V^{(t)}$ is an operational concept and not a true volume. Second, if a tissue has special affinity for a drug, the drug is sequestered in that tissue. Examples are sequestration of iodine by the thyroid gland and sequestration of calcium in bone. The sequestration in a particular tissue decreases the plasma concentration disproportionately, relative to the amount of the drug in the body. If the sequestration of a drug is marked, the estimate of V^{ss} of the drug may be larger than the volume of the whole body. Third, the space available for dilution is dependent on the chemical nature of the drug. Binding of a drug to proteins limits the dilution to the space that contains the proteins. Independent of binding to proteins, greater lipid solubility of a drug facilitates its crossing the cell membranes and increases the space available for dilution. It follows that V^{ss} for a more lipid-soluble drug is larger than V^{ss} for a drug that is less lipid soluble.

In conclusion, the separate consideration of dilution of a drug in the whole body leads to the concept of a space into which the drug is diluted. This space is characterized by its volume, hence the name "volume of distribution". The term describes the volume that would contain the total amount of a drug in the body were the concentration there uniform and equal to that in plasma at the same time. Although an artificial concept, volume of distribution is a useful one. It characterizes a drug or a group of drugs. However, it should be stressed that this volume is time-dependent. This fact necessitates that this volume be described by the semantically correct term $V^{(t)}$. When a drug is considered to be diluted in, but not lost from, the body, $V^{(t)}$ increases from V_C, at time $t = 0$ min, to a finite value V^{ss} at a later time. The rate of increase of $V^{(t)}$ is governed by k_{mix}.

Loss and dilution considered together. As mentioned earlier, loss of a drug from the body and dilution within the body occur concurrently. The goal of describing both processes together may be fulfilled by introducing two new concepts, that of a *pseudo-steady state* and that of a *fractional rate of loss.*

(1) The fact that the drug is lost continuously from the body indicates that a steady state cannot be achieved at any time after the bolus i.v. injection of a drug. When the mixing process is finished and when only the loss proceeds, a *pseudo-steady state* may be said to exist. The term implies that, although the plasma concentration is declining, it is declining in parallel with (at the same rate as) those that are presumed to exist elsewhere in the body. This implies also that the total *amount* of a drug in the body decreases at the same rate as the plasma concentration. Hence the ratio of this amount to plasma concentration is constant during the pseudo-steady state (fig. 2). If the amount of the drug in the body is postulated to be diluted uniformly in the "pseudo-steady state" space and the uniform concentration is assumed to be equal to the concentration in plasma at the same time, then the volume of this space may be calculated. In analogy to the process of mixing that established the concept of volume at steady state, V^{ss}, the simultaneous occurrence of both mixing and loss of the drug leads to the concept of yet another volume term. The volume of dilution at pseudo-steady state is termed the terminal volume, $V^{term.}$. The following consideration helps understand the size of this volume (fig. 2). As the drug is diluted progressively, it is lost simultaneously and continuously from the initial volume of dilution, V_C (see below). The loss is reflected in plasma concentrations that are smaller than if no loss occurred. Thus, although the dilution cannot progress beyond that given by V^{ss}, the *calculated* volume of dilution at pseudo-steady state, $V^{term.}$ is larger than V^{ss} because the amount of the drug in the body is related to the smaller plasma concentrations. By convention, the plasma concentration represents the concentration of the drug in V_C.

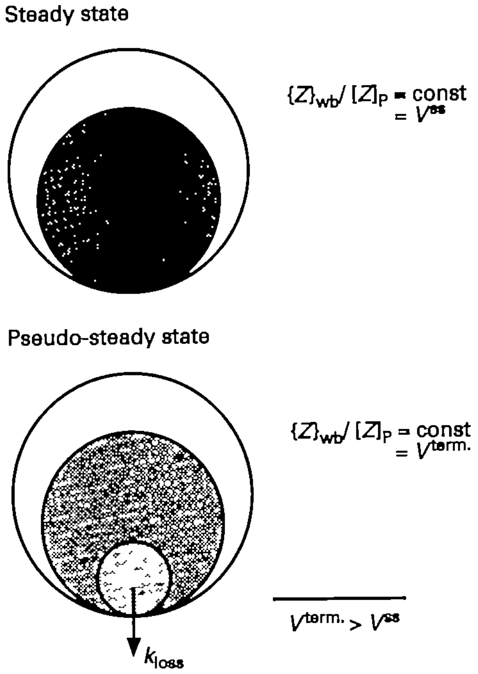
Steady state
$\{Z\}_{wb}/[Z]_P = \text{const} = V^{ss}$
Pseudo-steady state
$\{Z\}_{wb}/[Z]_P = \text{const} = V^{term.}$
$V^{term.} > V^{ss}$
k_{loss}

FIG. 2. *Definition of the volume of distribution at steady and at pseudo-steady state.* (Symbols as in figure 1.) When no loss of drug from the body occurs, the drug is eventually diluted into a space that does not change with time (= steady state). The initial dilution space (represented by the smallest circle) is the sampling site and the concentration there is given by the concentration in plasma, $[Z]_P$. The ratio of the amount of the drug in the body when steady state is reached ($\{Z\}_{wb}$) to the concentration of the drug in the initial dilution space at this time is constant. The value of this ratio defines the volume of the dilution space at steady state: it is named V^{ss}. When the drug is considered to be lost from the body, but the loss (arrow k_{loss}) is postulated to occur only from the initial space of dilution V_C, the drug is also eventually diluted into a space corresponding to V^{ss}. Because of the constant loss of drug from V_C, the concentration in this space is smaller than in the rest of the dilution space; the larger the value of the rate constant for loss k_{loss}, the larger this difference. The ratio of the amount of the drug in the body ($\{Z\}_{wb}$) to the smaller concentration in V_C eventually reaches a constant value and indicates that pseudo-steady state has been reached. The constant value of this ratio defines $V^{(t)}$ during the pseudo-steady state, $V^{term.}$. Thus although drug is eventually diluted into an identical space, loss of drug from V_C increases the *calculated* value of $V^{(t)}$ to greater than that of V^{ss}. $V^{(t)}$ at pseudo-steady state, $V^{term.}$, *appears* larger than $V^{(t)}$ at steady state, V^{ss}.

The concept of the time-dependent volume of distribution $V^{(t)}$ may now be expanded to include the loss of drug from the body and the mixing of drug within the body. The time profile of $V^{(t)}$ may be described as follows: $V^{(t)}$ increases from the initial value of V_C at time $t = 0$ min, reaches V^{SS} at some later time, and asymptotically approaches its maximal value, $V^{\text{term.}}$. The rate constants k_{loss} and k_{mix} govern the time profile of $V^{(t)}$ when the loss and mixing are considered together. The newly proposed term, $V^{\text{term.}}$, was previously—but less meaningfully—named V^{β} or V^{area}. After bolus injection of a drug, $V^{(t)}$ increases sequentially from V_C, to V^{SS}, to $V^{\text{term.}}$. Whereas $V^{(t)}$ only momentarily equals V_C and V^{SS}, it remains equal to $V^{\text{term.}}$ for as long as the pseudo-steady state exists.

(2) The separate consideration of loss of drug from the whole body neglects the fact that, at any given moment, not the total amount of drug is available for excretion, metabolism or both. Conceptually, only a portion of the total amount in the body is present in locations where these processes occur. It is assumed that these locations are contained within the initial space of dilution. In terms of likelihood, the probability of being lost from the body is given by k_{loss} if a drug molecule is present in this space and 0 if the molecule is present elsewhere in the body. This consideration reduces the overall chance that a molecule of the drug will be lost. This *fractional rate of loss* is formally accounted for by reducing the value of k_{loss}. Algebraically, this is accomplished by multiplying k_{loss} by the ratio of V_C to $V^{\text{term.}}$.

(3) When the two processes (loss from the body and mixing within it) are considered together, the time course of the plasma concentrations of a drug is influenced by both. Because, in the presence of loss, the mixing implies a dilution into the volume $V^{\text{term.}}$, the process of dilution is completed after a finite time, and thereafter the decrease in plasma concentrations reflects only loss of drug from the body. Accordingly, the plasma concentration shows two, more or less distinctive phases: the initial one, during which both loss and mixing proceed concurrently, and a later one, when the plasma concentration decreases only because of loss of drug from the body.

The absolute values for the rate constants for loss (k_{loss}) and mixing (k_{mix}) and their relative magnitudes determine how rapidly the plasma concentration decreases with time and how distinctive the two phases are. When both rate constants are large, the plasma concentrations decrease rapidly. If $k_{\text{mix}} \gg k_{\text{loss}}$, the process of dilution terminates early. The value of k_{loss} determines how rapidly the drug leaves the body: the larger the value of k_{loss}, the more rapid the decrease in plasma concentration (and decrease in the amount remaining in the body) during the whole sojourn of the drug in the body.

The reconstruction of the time course of the plasma concentrations of a drug is now partially complete and may be summarized by the following equation for the time course of the plasma concentration of the drug Z:

$$[Z]_P{}^t = X\cdot e^{-(k_{\text{loss}}+k_{\text{mix}})\cdot t} + Y\cdot e^{-\frac{V_C}{V^{\text{term.}}}\cdot k_{\text{loss}}\cdot t} \qquad (13)$$

The values for the two initial concentrations in plasma, X and Y, remain to be determined. Equation (13) is equivalent to equation (1) and shows the following identities:

$$\alpha = k_{\text{loss}} + k_{\text{mix}};\ \text{and}\ \beta = \frac{V_C}{V^{\text{term.}}}\cdot k_{\text{loss}} \qquad (14)$$

It is now evident that the exponents α and β in equations (1) and (3) are indeed hybrid rate constants composed of the two "primary" rate constants, k_{loss} and k_{mix}, and the two "primary" volume terms, V_C and $V^{\text{term.}}$. It is also evident that the concentration X disappears from plasma rapidly as a result of loss of drug from the body (given by k_{loss}) and its dilution within the body (given by k_{mix}). The concentration Y disappears at the fraction of the rate constant k_{loss} (since $V_C < V^{\text{term.}}$), and the rate of loss is not influenced by mixing.

No general solution of equation (13) is possible as long as the initial plasma concentrations X and Y are considered. The difficulty may be circumvented if equation (13) is converted into the form of equation (3). The conversion introduces explicitly the dose and V_C. The latter was used already to define β and does not represent a new entity.

$$[Z]_P{}^t = \frac{Dose_z}{V_C}\left(M\cdot e^{-(k_{\text{loss}}+k_{\text{mix}})\cdot t} + (1-M)\cdot e^{-\frac{V_C}{V^{\text{term.}}}\cdot k_{\text{loss}}\cdot t}\right) \qquad (15)$$

The task is now to express the fractions M and $(1-M)$ in terms of the known primary rate constants, k_{loss} and k_{mix}, and the primary volumes V_C and $V^{\text{term.}}$. The solution is found by defining $V^{\text{term.}}$ in terms of the area under the plasma concentration *vs* time curve (AUC). The definition was modified from the standard one [4] to conform to equation (3):

$$V^{\text{term.}} = \frac{V_C}{\beta\cdot\left(\dfrac{M}{\alpha}+\dfrac{1-M}{\beta}\right)} \qquad (16)$$

Substitution of α and β by their newly derived values (from equation (14)) yields the following expressions for M and $(1-M)$:

$$M = \frac{(k_{\text{loss}}+k_{\text{mix}})\cdot(V_C - V^{\text{term.}})}{V_C\cdot k_{\text{loss}} - V^{\text{term.}}\cdot(k_{\text{loss}}+k_{\text{mix}})} \qquad (17)$$

$$1-M = \frac{V_C\cdot k_{\text{mix}}}{V^{\text{term.}}\cdot(k_{\text{loss}}+k_{\text{mix}}) - V_C\cdot k_{\text{loss}}} \qquad (18)$$

The defined values for M and $(1-M)$ have no units and represent the fractions of the administered dose that disappear from plasma at different rates. Their complete definition is given exclusively in those terms that were used earlier to define the exponents in equation (3). The expression for M appears rather complex. Its dependency on the four primary variables is as follows: when three of these are held constant and only the fourth is changed, then the value of M increases with increasing k_{loss} and $V^{\text{term.}}$, but decreases with increasing k_{mix} and V_C.

V^{SS} also may be given in terms of the primary variables. If, in the standard expression for V^{SS} [4], the values for A, B, α and β are substituted by their newly derived equivalents, V^{ss} is defined as:

$$V^{ss} = \frac{V_C \cdot k_{loss} + V^{term.} \cdot k_{mix}}{k_{loss} + k_{mix}} \tag{19}$$

This demonstrates that the value for V^{ss} is dependent on, and may be defined by, the primary variables.

Although it is also possible to define the time course of $V^{(t)}$ in terms of k_{loss}, k_{mix}, V_C and $V^{term.}$, the final expression is rather complex and offers no advantage over the definition of $V^{(t)}$ proposed by Niazi [6] in terms of the dose, A, B, α and β (equation (1)). In terms of equation (3), $V^{(t)}$ is given by:

$$V^{(t)} = V_C \cdot \frac{\dfrac{M}{\alpha} \cdot e^{-\alpha \cdot t} + \dfrac{1-M}{\beta} \cdot e^{-\beta \cdot t}}{\left(\dfrac{M}{\alpha} + \dfrac{1-M}{\beta}\right) \cdot (M \cdot e^{-\alpha \cdot t} + (1-M) \cdot e^{-\beta \cdot t})} \tag{20}$$

The concurrent loss from, and dilution within, the body require that the systemic clearance of a drug, Cl_{sys}, be redefined. In analogy to equation (9), the loss may be considered to occur either from the initial dilution space of volume V_C with the rate constant k_{loss} or from the dilution space of volume $V^{term.}$ during the pseudo-steady state and the rate constant β ($\beta = (V_C/V^{term.}) \cdot k_{loss}$). Therefore, the two expressions for systemic clearance, Cl_{sys}, are equivalent:

$$Cl_{sys} = V_C \cdot k_{loss} \text{ or } Cl_{sys} = V^{term.} \cdot \beta \tag{21}$$

CONCLUSION

The customary *description* of the biexponential time course of the plasma concentration of a drug is given by equation (1) in terms of the administered dose and four descriptors (A, B, α and β). Two of these are dose-dependent (A and B) (table I). The four parameters for the biexponential decay are V_C, M, α and β. The decay is described optimally by equation (3). The description is dependent on the assumptions that plasma concentration increases in proportion to the increase in dose (the assumption of linear pharmacokinetics) and that the experimental data are adequately and appropriately represented by a biexponential function. It is now evident that a complete report of a biexponential decay of the plasma concentration must provide either the dose and the four descriptors or the four parameters. Reporting only the rate constants α and β is insufficient and does not allow the reader to form an "image" of the time course of the plasma concentrations.

TABLE I. *Description of the biexponential decay of the plasma concentrations for drug Z. †Systemic clearance is defined only if drug is lost from the central compartment* ($Cl_{sys} = V_C \cdot k_{Co}$). *The postulate that loss occurs exclusively from the peripheral compartment precludes calculation of* Cl_{sys}

Dose-dependent description:

$$C = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}$$

Dose-independent description:

$$[Z]_P{}^t = \frac{Dose_z}{V_C}(M \cdot e^{-\alpha \cdot t} + (1-M) \cdot e^{-\beta \cdot t})$$

Parameters of the biexpoential description: V_C, M, α and β

Interpretation of the biexponential decay

Compartmental interpretation		Whole body interpretation	
Parameter	Unit	Parameter	Unit
V_C	litre kg^{-1}	V_C	litre kg^{-1}
k_{Co} or k_{po}	min^{-1}	k_{loss}	min^{-1}
k_{Cp}	min^{-1}	k_{mix}	min^{-1}
k_{pC}	min^{-1}	$V^{term.}$	litre kg^{-1}
Derived variables			
Cl_{sys}†	litre kg^{-1} min^{-1}	Cl_{sys}	litre kg^{-1} min^{-1}
		V^{ss}	litre kg^{-1}

An *interpretation* of the biexponential decay is based on a set of assumptions specific for that interpretation and the above four parameters (table I). Independent of which method is selected to interpret the biexponential decay, the number of parameters used in the interpretation cannot exceed the number of parameters provided by the description of the data. The two available interpretations postulate that the transport and elimination of the drug proceed as first-order processes.

If the *compartmental interpretation* is selected, at least two compartments must be postulated such that the drug is transported reversibly between them. The term compartment refers to an *amount* of a drug in the body that acts kinetically as a distinct and well-mixed entity [7]. Specifically, the term compartment may not be understood as either a concentration or a volume. In the two-compartment model, the amounts are named the central (C) and the peripheral (p) compartment. The model must also identify the compartment or compartments from which the drug is eliminated. Four parameters are necessary to characterize the two-compartment model (table I): the volume of the central compartment, V_C, and three "micro" rate constants. Two of these describe the intercompartmental transport (generally denoted k_{Cp} and k_{pC}), and one describes the elimination to "outside" (o) (either k_{Co}, if the elimination occurs from the central, or k_{po}, if the elimination occurs from the peripheral compartment). The assumptions that the drug is injected into the central compartment where it achieves instantaneously a uniform concentration, and that blood samples are collected from this compartment, allow the calculation of the volume of the central compartment. The data on the time course of the plasma concentrations alone are not sufficient to define the two-compartment model if the drug is postulated to be eliminated from each of the two compartments at different rates. The postulate of two independent rates of elimination would require a fifth parameter that is not available from the description of the biexponential decay.

The "*whole body*" *interpretation* is based on the assumptions that the drug is eliminated only from the initial space of distribution and that it is *uniformly* diluted in the body. The interpretation uses four parameters (table I). Two of these are first-order rate constants, one for loss of drug from the body, k_{loss}, and the other for dilution of drug in the body, k_{mix}. The two remaining parameters are volume terms, one defining the volume of the initial dilution space, V_C, and the other the volume of the terminal dilution space, $V^{\text{term.}}$. The caveats in interpreting these volumes as real physiological entities should, however, be kept in mind.

The details of deriving the parameters for the whole body interpretation may be summarized as follows. After a biexponential function is found to fit the experimental data for the decay of the plasma concentrations of a drug, a function in the form of equation (1) is obtained along with the four descriptors: A, B, α and β. The calculation of V_C (equation (2)) and of M allows the time course to be presented in a better comprehensible, parametric form (equation (3)). The three remaining parameters for the whole body interpretation are calculated as the last step in the analysis. $V^{\text{term.}}$ is derived from equation (16). Definition of V_C and $V^{\text{term.}}$ permits calculation of k_{loss} and k_{mix}:

$$k_{\text{loss}} = \beta \cdot \frac{V^{\text{term.}}}{V_C} \text{ and } k_{\text{mix}} = \alpha - k_{\text{loss}}$$

The values for V^{SS} and Cl_{sys} are derived from equations (19) and (21), respectively.

The analysis of the time course of the plasma concentration in terms of the area under the plasma concentration *vs* time curve (AUC, and its time integral, AUMC) [4] deliberately avoids the issue of whether a biexponential function is appropriate to describe the decay of the plasma concentration. Unless the biexponential decay is established independently, characterization of the plasma concentration in terms of AUC and AUMC precludes calculation of the primary rate constants that are required for the whole body interpretation. The values for Cl_{sys}, V^{SS} and $V^{\text{term.}}$ (or its equivalent V^{area}) as calculated by this analytical method have, however, the same meaning as those defined here for the whole body interpretation of the biexponential decay.

It is of interest that the compartmental and whole-body interpretations share one, and only one, parameter: V_C. The rate constant k_{loss} is conceptually equivalent to the rate constant k_{C0} only if the drug is assumed to be eliminated from the central compartment. The whole body interpretation is inappropriate if a drug is postulated to be eliminated from the peripheral compartment with the rate constant k_{p0}. The rate constant k_{mix} and the concept of the time-dependent volume of distribution $V^{(t)}$ cannot be addressed in terms of the compartmental interpretation. First, the concept of volume of distribution implies a *uniform* concentration within the body. Moreover, $V^{(t)}$ may be defined only if it is assumed that the uniform concentration is equal to that in plasma—that is, in V_C. The concept of $V^{(t)}$ is, hence, incompatible with the concept of separate and distinct amounts of a drug within the body. Specifically, the terms V^{SS} and $V^{\text{term.}}$ (or V^{area} or V^{β}) are inappropriate in the context of compartmental interpretation. Identifying the sum of the unknown compartmental volumes with $V^{(t)}$—at any time after the injection—runs contrary to the assumptions of both interpretations. Second, the volumes of the compartments are conceived as constant. The volume of the peripheral compartment cannot be defined explicitly. The frequently cited expression for its calculation ($V_p = V_C \cdot (k_{Cp}/k_{pC})$, is based on the false premise that the rates of transfer between the two compartments may be expressed in clearance terms. Compartmental interpretation provides information about the *amount* of drug in the peripheral compartment but, without additional information, the amount cannot be resolved into its two constituent factors—concentration and volume. Further, the definition of this volume would represent a fifth parameter in the compartmental interpretation. As mentioned earlier, a fifth parameter is not available from the description of the biexponential decay.

The distinct advantage of the compartmental interpretation is the option to consider separate *amounts* of a drug within the body. The advantage is not dependent on the definition of the compartmental volumes. In contrast, the whole body interpretation offers the concept of a space of dilution characterized by its volume, $V^{(t)}$, but the concentration throughout this space is assumed to be uniform and equal to that in plasma. The investigator may choose one or other method of interpretation, but the parameters of the two interpretations are not interchangeable.

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CORRESPONDENCE

PREDICTION OF ARTERIAL P_{CO_2} FROM END-TIDAL P_{CO_2}

Sir,—In his abstract [1] Dr Fletcher described a series of experiments to test the hypothesis that the arterial–end-tidal P_{CO_2} difference ($Pa_{CO_2} - P\text{E}'_{CO_2}$) during anaesthesia and controlled ventilation can be predicted by what happens to end-tidal P_{CO_2} when the ventilator frequency and tidal volume are changed. Such a prediction is important because the value of ($Pa_{CO_2} - P\text{E}'_{CO_2}$) is thought to represent the degree of spatial inhomogeneity of ventilation and perfusion ($\dot{V}/\dot{Q}$ mismatch).

The results of these experiments show that patients with a greater degree of $\dot{V}/\dot{Q}$ mismatch, as shown by a greater initial value of ($Pa_{CO_2} - P\text{E}'_{CO_2}$), displayed a greater increase in $P\text{E}'_{CO_2}$ when the tidal volume increased and ventilation frequency reduced simultaneously. From these results, the author suggested that patients with an increased ($Pa_{CO_2} - P\text{E}'_{CO_2}$) can be predicted by performing this manoeuvre.

In my view, these data should be interpreted more cautiously.

First, it is the value of ($Pa_{CO_2} - P\bar{\text{A}}_{CO_2}$) rather than ($Pa_{CO_2} - P\text{E}'_{CO_2}$) which more accurately reflects $\dot{V}/\dot{Q}$ mismatch, where Pa_{CO_2} = flow-weighted average end-capillary P_{CO_2} and $P\bar{\text{A}}_{CO_2}$ = ventilation-weighted average alveolar P_{CO_2}, of all the alveolar units.

Second, it can be shown from a mathematical model, and from experimental data, that at least some change in $P\text{E}'_{CO_2}$ in response to an alteration in ventilation rate and frequency is expected, even if there is *complete homogeneity* of ventilation and perfusion.

The reduction in $P\text{E}'_{CO_2}$ seen in some patients after this manoeuvre might be explained by the fact that, by doubling the tidal volume and halving the frequency, there is a net increase in alveolar ventilation rate, as the deadspace ventilation rate has been reduced.

The increase in $P\text{E}'_{CO_2}$ in other patients is also explicable to some extent, as follows. It has been appreciated for many years that alveolar and arterial P_{CO_2} vary within the ventilatory cycle [2, 3]. $P\text{A}_{CO_2}$ increases during expiration, and its time course is exponential [4]. As the decay in flow rate in expiration is also exponential, the value of the differential, $\text{d}P\text{A}_{CO_2}/\text{d}V$ is constant. This phenomenon is seen when airway P_{CO_2} is plotted against expired volume (fig. 1). In this plot, deadspace at the beginning of the breath ($V\text{D}_\text{i}$) differs slightly from the deadspace at the end of the breath ($V\text{D}_\text{f}$) which has been extrapolated, since $V\text{D}$ varies with $V\text{T}$. The "trough" value of the oscillation ($P\text{I}'$) represents alveolar P_{CO_2} at the end of inspiration. Peak expiratory alveolar P_{CO_2} ($P\text{A}$, peak) is constructed by extrapolation of the "plateau". The slope of this plateau ($\text{d}P/\text{d}V$) is seen to be constant. Using this model, the mean alveolar P_{CO_2} ($P\bar{\text{A}}$) can be determined [5].

From the geometry of the above plot, the following equation can be derived:

$$P\text{E}' = \left(\frac{V\text{T}}{2} - V\text{D}_\text{f}\right)\cdot \text{d}P/\text{d}V + P\bar{\text{A}} \qquad (1)$$

If $\dot{V}/\dot{Q}$ mismatching was zero, doubling $V\text{T}$ and reducing the ventilation frequency (such that the constancy of alveolar ventilation was maintained) would have no effect on $P\bar{\text{A}}$, which would be a constant in equation (1). As $V\text{D}_\text{f}$ and $\text{d}P/\text{d}V$ are also constant, $P\text{E}'$ varies linearly with $V\text{T}$.

If the tidal volume is greater than twice the deadspace, $P\text{E}' > P\bar{\text{A}}$. Similarly, if tidal volume is less than twice the deadspace, $P\bar{\text{A}} > P\text{E}'$.

In the following experiment, airway carbon dioxide was measured using a real-time mainstream capnometer (HP 47210A, Hewlett-Packard, Waltham, MA, U.S.A.). Expiratory volume was measured by computerized integration of the flow signal from a Hewlett-Packard pneumotachograph. These devices were calibrated with a "Haldane" reference gas and large syringe, respectively.

For a series of consecutive breaths of increasing volume in a young healthy subject, the difference between true mean alveolar P_{CO_2} and end-tidal P_{CO_2} ($P\text{E}'_{CO_2} - P\bar{\text{A}}_{CO_2}$) was plotted against tidal volume, breath by breath (fig. 2).

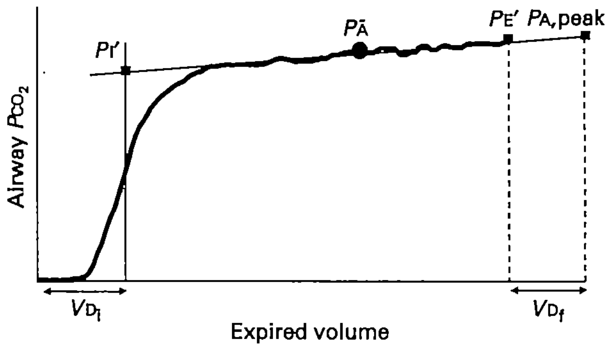

FIG. 1. Relationship between airway P_{CO_2} and expired volume. $V\text{D}_\text{I}$ = deadspace at the beginning of the breath; $V\text{D}_\text{f}$ = deadspace at the end of the breath; $P\text{I}'$ = "trough" value of the oscillation; $P\text{E}'$ = end-tidal P_{CO_2}; $P\text{A}$,peak = peak expiratory alveolar P_{CO_2}.

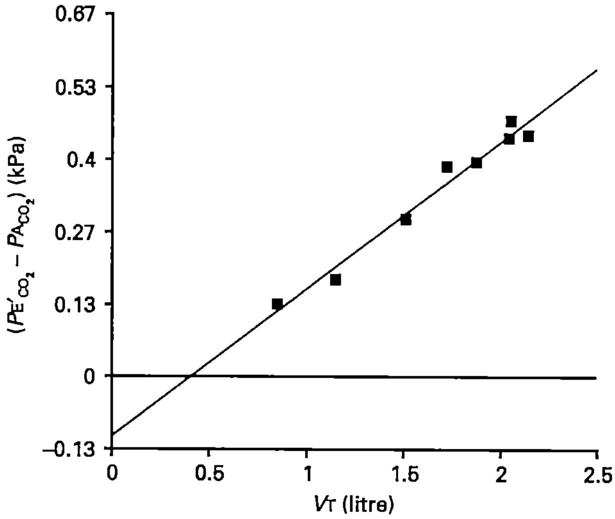

FIG. 2. Plot of difference between end-tidal and mean alveolar P_{CO_2} ($P\text{E}'_{CO_2} - P\text{A}_{CO_2}$) as a function of tidal volume ($V\text{T}$). Regression equation: ($P\text{E}'_{CO_2} - P\text{A}_{CO_2}$) = $2.03V\text{T} - 0.82$; $r = 0.987$; $P < 0.0001$. Regression coefficient = 2.03; $P = 0.000$.

From this plot it can be seen that the end-tidal–mean alveolar discrepancy increases linearly with tidal volume. The intercept of the regression line on the *x* axis is $2V\text{D}$ (0.4 litre) and the slope of the regression line is ($\text{d}P/\text{d}V$)/2.

$\text{d}P/\text{d}V$ was seen to be constant within breaths, and between breaths ($P < 0.0001$) for a particular individual. However, because $\text{d}P/\text{d}V$ is related to certain properties of an individual's "flow–volume loop", it shows a greater *inter-individual* variation and is likely to be greater in patients with obstructive airways disease, in whom an increase in tidal volume might produce a greater increase in ($P\text{E}'_{CO_2} - P\bar{\text{A}}_{CO_2}$).

From this model and these data, it seems that any change in $P\text{E}'_{CO_2}$ in response to a change in ventilation pattern, in addition to the component proposed by Fletcher (resulting from inter-individual variation in $\dot{V}/\dot{Q}$ spread) has a significant component arising from the fact that, by virtue of the ventilatory oscillation of P_{CO_2}, $P\text{E}'_{CO_2}$ varies with tidal volume in a manner independent of $\dot{V}/\dot{Q}$ homogeneity.

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Sir,—Thank you for the opportunity to reply to Dr Farmery, whose comments I appreciate. He suggests that my observations on what happens to end-tidal $P\text{CO}_2$ when tidal volume is doubled and frequency halved [1] should be more cautiously interpreted. The work was preceeded by a pilot study of 30 patients, which I presented at the Edinburgh Anaesthesia Festival but did not publish because my capnograph and blood-gas analyser had not been calibrated with the same gas. Nevertheless, that series showed qualitatively the same result as the present one. For this reason I can confidently say that, *whatever the mechanism involved*, patients with large $(Pa_{CO_2} - P\text{E}'_{CO_2})$ values at a ventilatory frequency of 20 b.p.m. do indeed show a considerable increase in $P\text{E}'_{CO_2}$ when the ventilator setting is changed as above. Patients with small $(Pa_{CO_2} - P\text{E}'_{CO_2})$ values show a decrease in $P\text{E}'_{CO_2}$.

What happens in patients with small $\dot{V}/\dot{Q}$ spread? Increasing tidal volume at the same end-expiratory lung volume hardly affects the airway deadspace [2]. Airway deadspace ventilation is thus halved, and so effective ventilation $((V\text{T} - V\text{D}_1)$ in Dr Farmery's illustration) and alveolar ventilation (the area under the curve) are increased. $P\text{E}'_{CO_2}$ must therefore be reduced, whilst at the same time more carbon dioxide is excreted. This is particularly true of Dr Farmery's hypothetical patient with zero $\dot{V}/\dot{Q}$ spread; but this hypothetical patient has virtually no phase III slope—I have recorded carbon dioxide tracings in many such patients, children and young adults—and no increase in $P\text{E}'_{CO_2}$ was seen on increasing $V\text{T}$. Cyclical variation in $P\text{A}_{CO_2}$ cannot be important here.

In patients with large $(Pa_{CO_2} - P\text{E}'_{CO_2})$ values—that is, those with large $\dot{V}/\dot{Q}$ spread, changing the ventilator setting as above causes $P\text{E}'_{CO_2}$ to increase by 0.2–0.4 kPa. My explanation, that poorly ventilated, small $\dot{V}/\dot{Q}$ alveoli particularly benefit from the change in ventilatory pattern, is based largely on the work of West and colleagues [3, 4] and on my own studies [2, 5]. We do not know for certain if spatial $\dot{V}/\dot{Q}$ variation (between units) is more important than temporal (within-units) variation. However, one indication of the relative roles of the two forms of $\dot{V}/\dot{Q}$ mismatch is that the alveolar deadspace fraction is greatly reduced when tidal volume is increased and frequency reduced [2]. This would not have been the case had cyclical $\dot{V}/\dot{Q}$ variation been important at large tidal volumes.

The most striking increases in $P\text{E}'_{CO_2}$ are seen in patients with severe expiratory obstruction—that is, patients with intrinsic PEEP or auto-PEEP. In these, if the ventilator setting is momentarily increased early in expiration, extending *expiratory time* but not *inspiratory volume* for that breath, $P\text{E}'_{CO_2}$ increases and the volume of carbon dioxide in that breath is greatly increased. This suggests that a significant volume of increased $P\text{CO}_2$ compartments were present at the old ventilator setting, but that they were poorly ventilated so that their contributions did not reach the airway opening. (I showed tracings from such a patient when I presented the paper.) A second time line of proof, obtained from the patients demonstrated in paper [2] is that those patients who show the greatest change in $(Pa_{CO_2} - P\text{E}'_{CO_2})$ when the ventilator is changed are those with the greatest deadspace.

Therefore I believe that, in such patients, spatial variation in $\dot{V}/\dot{Q}$ is important. However, Brew's mathematical model of changes in alveolar carbon dioxide partial pressure during passive ventilation [5] shows that alveolar $P\text{A}_{CO_2}$ does in fact increase more steeply in lungs with increased time constants. To extend West's work: the alveoli that empty last have *two* reasons to have the greatest $P\text{CO}_2$.

Dr Farmery's experiments confirm the theory put forward previously on the effects of tidal volume on the difference between mean alveolar $P\text{CO}_2$ $(P\text{A}_{CO_2})$ and $P\text{E}'_{CO_2}$ [5]. I take the point that this difference is a better indicator of $\dot{V}/\dot{Q}$ spread than $(Pa_{CO_2} - P\text{E}'_{CO_2})$. However, having spent 13 years since the publication of my thesis [6] failing almost totally to get the (to my mind) simpler and more usable concept of alveolar deadspace fraction accepted by the respiratory physiological fraternity, I am not hopeful about publishing anything as advanced as $P\text{A}_{CO_2}$; end-tidal $P\text{CO}_2$ is apparently sufficient for most readers. Also, the object of the present paper was to produce an idea which had clinical appeal, and therefore it was logical to use $P\text{E}'_{CO_2}$.

Dr Farmery states that the "slope of the plateau", is constant. This often appears to be the case, but in my thesis [6] I mentioned two situations in which phase III was concave—that is, the slope increased with $V\text{T}$: severe expiratory obstruction and gross obesity. In the former case, I believe that changes in alveolar $P\text{CO}_2$ contribute to the concavity.

In conclusion, Dr Farmery is correct to mention a second reason for the increase in $P\text{E}_{CO_2}$ which can be seen in patients with poor lung function; the constraints of the abstract prevented me from making the point there. While cyclical variation in $P\text{A}_{CO_2}$ is of no significance in patients with good lung function, it may be of significance in those with poor function [5]. I have presented evidence that increased $P\text{CO}_2$ compartments are present in patients with increased $(Pa_{CO_2} - P\text{E}'_{CO_2})$.

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SUXAMETHONIUM IN DAY-CASE ANAESTHESIA

Sir,—I read with interest the paper by Alcock and colleagues [1] on intubation for day-case dental anaesthesia. I was surprised that suxamethonium should still be advocated as the neuromuscular blocking drug of choice for this procedure. The authors quoted rates of postoperative myalgia of up to 85%, and in their study 74% of patients reported myalgia and 42% of these suffered severe pain.

Is this really acceptable for a day-case procedure? The use of short-acting, non-depolarizing neuromuscular blocking drugs such as atracurium or vecuronium would allow excellent intubating conditions with no postoperative myalgia [2, 3]. In an unpublished study, I found no postoperative myalgia after vecuronium or atracurium, but 85% after suxamethonium. I have abandoned the use of suxamethonium in day-case procedures, and I cannot believe that its further use in this situation can be justified.

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undergoing laparoscopy. *Anaesthesia and Intensive Care* 1987; 15: 310–316.

CORRELATION OF CHILD'S AGE WITH INFUSION RATES OF MIVACURIUM

Sir,—In the summary of their paper about infusions of mivacurium in children [1], Meretoja and Olkkola claim "a significant negative correlation between infusion rate and age of a patient". There are no figures in the Summary to support this, and the statistical support is weak. For 95 % neuromuscular block, the regression gave $P = 0.0553$, which is outside what they regarded as significant ($P < 0.05$). At 50 % neuromuscular block, regression gave $P = 0.0197$, but this lesser probability was caused largely by an outlier.

Their data were re-analysed (StatviewSE+Graphics; Macintosh LCII). Without the outlier, the probability of the regression for 50 % neuromuscular block reduces to 0.034 (table I). Meretoja and Olkkola drew only the best-fit regression lines on their figure, but the 95 % confidence intervals on the slopes are wide (fig. 1). Removing the outlier narrows the confidence intervals (although the interval includes a slope of zero at 95 % block even with the outlier) but reduces the slope (fig. 1, table I),—that is, reduces the apparent dependence of infusion rate on age.

Removing an outlier is risky unless there is good reason to doubt it is a "true" observation, but least squares linear regression analysis requires that the data be distributed normally. If the outlier is "true", then a curvilinear function must be applied—although that is not valid with only a single point to support the relation. In fact, any relation between infusion rate and age *must* be curvilinear in the limit because extrapolation of Meretoja and Olkkola's line for 50 % block gives an infusion rate of zero at 28 yr.

The investigators wrote, "a significant correlation between infusion requirement and age is clinically important". Supposing this relation is true over the range of ages studied, it is clinically important only if clinicians can use the regression to estimate drug need, but the large scatter of data (which the investigators acknowledge) makes this difficult.

Figure 1 also shows the 2SD range either side of the regression line (outlier removed). The range at age 1 yr (about 230–570 $\mu g\ kg^{-1}\ h^{-1}$ for 50 % block) overlaps considerably the range at 15 yr (about 100–440 $\mu g\ kg^{-1}\ h^{-1}$). If the outlier is included, the lines are steeper, which increases the infusion difference with age, but the 2SD range is wider. If more children had been studied, this would have reduced the confidence intervals on the slope (although we do not *know* that there would still be a significant slope), but the scatter would have remained much the same.

This is not to say that there is *not* a negative correlation of infusion rate with age, but that the certainty of the correlation is less than the investigators suggest. Looking at onset time, which they measured as time to maximal block, and age (their figure 1), this regression is also exaggerated by an outlier, but these data are more robust than the data on infusion rate: the regression coefficient of 0.14 (95 % CL 0.06, 0.23) becomes 0.09 (0.02, 0.16) if the outlier is removed. However, as with infusion rate, in the limit the relation must be curvilinear: at age 50 yr, time to maximal block is unlikely to be 9 min so the outlier is pulling the regression in the "wrong" direction, unlike the outlier for infusion rate, which is pulling the regressions in the direction consistent with the investigators' hypothesis.

Meretoja and Olkkola's concluding statement that "Infusion requirement was greatest and onset time least in younger patients" needs confirmation.

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TABLE I. *Least squares linear regression analysis of data of Meretoja and Olkkola [1]. Regression of infusion requirement for two degrees of neuromuscular block (50 % NMB and 95 % NMB) on age of child: infusion rate = (slope × age) + intercept. Two sets of statistics are shown: original (direct from Meretoja and Olkkola); minus outlier (point arrowed in fig. 1 deleted). Bracketed figures for slope are the 95 % confidence intervals (not given by Meretoja and Olkkola). r = Correlation coefficient; P = probability (given to 2 significant figures)*

	Slope	Intercept	*r*	*P*
50 % NMB				
Original	−17 (−30, −3.0)	470	0.51	0.020
Minus outlier	−11 (−20, −0.9)	406	0.47	0.034
95 % NMB				
Original	−33 (−66, 0.9)	1180	0.42	0.055
Minus outlier	−18 (−41, 5.7)	1022	0.35	0.13

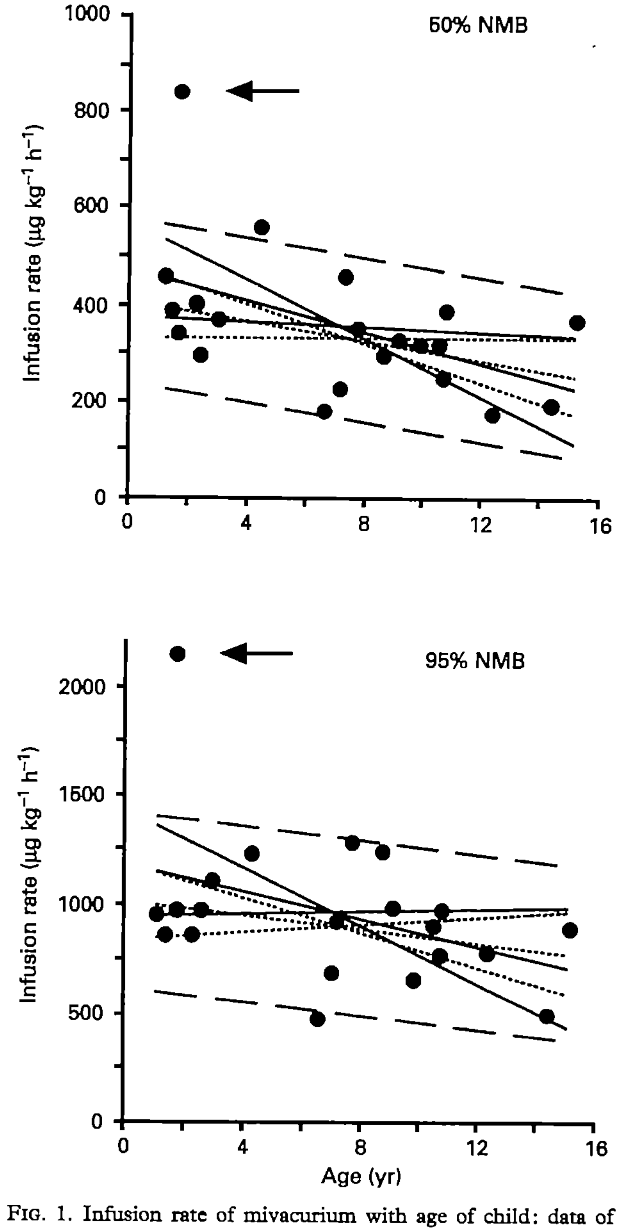

FIG. 1. Infusion rate of mivacurium with age of child: data of Meretoja and Olkkola [1]. Upper panel: 50 % neuromuscular block; lower panel: 95 % neuromuscular block. Solid lines are the regression through all the points; dotted lines are the regression with the arrowed outlier removed: lines of best fit and 95 % confidence limits on slopes shown. The dashed lines are the 2SD ranges around the dotted lines of best fit.

Sir,—Dr Goodman has raised the important issue of removing a possible outlier from a scientific material. There are both statistical and ethical aspects of this problem. It could be acceptable to remove a single value which is outside 3SD from the mean, provided that one describes the "outlier" in the results. However, we demonstrated that both the infusion requirement of mivacurium to maintain a 50% neuromuscular block and the onset time of mivacurium were dependent on age [1]. Dr Goodman suggests that we should have removed one patient from both of these data sets. We felt that this was not justified as we could not identify a reason why these patients were exceptional in their response, and because statistically significant regression persisted after these two patients were removed from the regression lines, as noticed also by Dr Goodman.

Furthermore, we felt that our findings are clinically important. Clinicians should appreciate that the infusion requirement of mivacurium is even greater in younger children than in older children, and onset time is shortest in youngest children. Our regression lines should not be used to predict any individual's response because of the wide individual variation in the responses. Variability in infusion rate was found also in other paediatric studies [2, 3]. It is of interest that one of these studies analysed age-dependence of infusion requirement of mivacurium in children, and also found a significant negative correlation [3]. Also, in our new series of 40 children aged 1–15 yr, a negative correlation existed between age and infusion requirement of mivacurium to maintain a 90% neuromuscular block ($I^{ss}_{90} = -34 \times \text{Age} + 1000\ \mu\text{g kg}^{-1}\ \text{h}^{-1}$; $r = 0.514$; $P = 0.0007$) [Meretoja and colleagues, unpublished data]. Thus it seems that our conclusions are valid.

Our data on the onset time of mivacurium are consistent with previous findings with other neuromuscular blocking drugs [4–6]. Short onset time is likely to be caused by a short circulation time, which is a physiological characteristic of children [7].

Regression analysis should not be used to make predictions outside the range of the independent variable. Dr Goodman is setting up a straw man when he estimates infusion rates and onset times far beyond the age range of our patients. It is clearly not appropriate to predict infusion rates or onset times for neonates or adults on the basis of our published data from children aged 1–15 yr [1].

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FENTANYL AND THE EXTRADURAL SIEVE

Sir,—Dr Tehan's report [1] prompts us to describe a similar event.

A 35-yr-old primipara presented at term in spontaneous labour. She had previously undergone excision of a small subserous uterine myoma, but was not felt to have decreased uterine integrity as a result. After 8 h of effective contractions, she had reached 4 cm of cervical dilatation. An extradural catheter was placed at the L2–3 interspace, and good analgesia obtained with 0.25% bupivacaine 9 ml and fentanyl 100 µg. A continuous infusion of 0.2% bupivacaine with fentanyl 2 $\mu\text{g ml}^{-1}$ at 9 ml h^{-1} was commenced and provided good analgesia for the next 8 h. Fourteen hours into labour, the fetal heart rate began to show intermittent late decelerations and lack of baseline variability. The infant was delivered by urgent Caesarean section. At no time after placement of the extradural did the mother experience breakthrough pain. At laparotomy, a complete placental abruption and rupture of the uterus into the left broad ligament were found.

The extent to which the opioid component of this patient's extradural analgesia masked the clinical signs of the uterine rupture and placental abruption is a matter for speculation. Our patient received extradural fentanyl from the outset, and we were thus unable to demonstrate any "extradural sieve" that might have been present. We agree that the safety of extradural opioids in labouring patients with a scarred uterus would provide an interesting subject for further study.

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1. Tehan B. Abolition of the extradural sieve by addition of fentanyl to extradural bupivacaine. *British Journal of Anaesthesia* 1992; **69**: 520–521.

IVOX, OXYGEN BALANCE AND THE HEART

Sir,—The Editorial on IVOX [1] referred to some of the potential gains from this technique in acute pulmonary failure. They include a reduction in mechanical lung damage, a reduction in the minimum inspired oxygen concentration and, perhaps most significant, an improvement in gas exchange. At this early stage of its development it seems important to differentiate clearly between hypoxia and hypoxaemia and, ideally, to use oxygen balance as the yardstick to assess any benefit from an increase in arterial oxygen content.

Unfortunately, there is still no reliable, sensitive and real-time method for determining global and regional oxygen debt, and intramucosal gastric pH (pHi) monitoring [2] has yet to be firmly established as a more reliable guide to global oxygen balance than the uncertainties of blood lactate. Despite these limitations, it seems fair to require a swift improvement in total oxygen uptake, lactic acidosis, or a small pHi, as certain evidence of a beneficial effect on oxygen balance from an increase in arterial oxygenation with the use of IVOX in critically ill patients, although an attributable reversal of depressed organ function [3] (for example improved haemodynamics and urine output) may currently be the only favourable sign when lactate and pHi are normal.

Theoretically, the oxygen content of jugular venous blood might also be helpful in this context. An increase with IVOX would signify a reduction in oxygen extraction and suggest the patient was hypoxaemic rather than hypoxic, his oxygen demand now being satisfied partially by an increase in the oxygen content of mixed venous blood. Where oxygen extraction is defective and fixed, as in pathological supply dependency from sepsis or the adult respiratory distress syndrome, there might be no change in jugular venous oxygen content, whatever the impact of IVOX on oxygen balance.

Besides improving its oxygenation, enhancement of oxygen uptake and correction of hypoxaemia might also have an indirect beneficial effect on the heart by reducing its workload, an especially valuable effect if the workload is made greater by an increased oxygen demand and the heart is depressed by disease or sepsis. However, if the patient remains hypoxic and supply-dependent despite correction of hypoxaemia, it seems unlikely that cardiac workload would decline. Measuring such benefit would obviously demand special monitoring. At the moment, most reports on IVOX [4–7] do not seem to address these considerations, but unless we approach IVOX in this critical way we may continue to confuse hypoxaemia with hypoxia and generate the same unjustified enthusiasm for its impact on oxygen balance in acute respiratory failure as many clinicians still have for positive end-expiratory pressure (PEEP) [8].

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VENOUS AIR EMBOLISM WITH A WATER JET DISSECTOR

Sir,—We read with interest the article by Dr Smith [1], reporting an incident of apparent major air embolism occurring during hepatic resection using a water jet dissector.

We have introduced a water jet dissector (Hepatotom) [2–4] at the Clinic of Visceral and Transplantation Surgery, University of Bern, Switzerland and since 1989 have performed about 50 liver resections with it. Air embolism during hepatic resection is a result of injury to large intrahepatic veins during parenchymal dissection. Negative or low hepatic i.v. pressure results in air being aspirated into these veins. Embolism might also result from cutting more superficially situated veins and presumably this could occur even with injury to smaller veins.

Interestingly, Mastragelopulos and colleagues [5] reported on argon gas embolism occurring during laparoscopic cholecystectomy and coagulation of the liver bed with the Argon Beam Coagulator. The authors recommended caution and suggested keeping the instrument a reasonable distance from vessels and allowing for possible vessel anomalies, with relatively large vessels being close to the liver surface. The same precautions are necessary during use of the water jet dissector.

The report by Dr Smith stated specifically that during parenchymal transsection their patient was in a supine position with a 30° head-up tilt. This is potentially dangerous during liver resection of any kind and we recommend that during the parenchymal phase of the operation the patient should be in a Trendelenburg position of about 15°. This mandatory central venous hypotension is used during parenchymal transsection. This technique averts the risk of air or gas embolism. Using this approach, the danger of air embolism during parenchymal dissection is minimal and one of us (L.H.B.) has performed 150 major hepatic resections without such an incident.

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Sir,—Thank you for the opportunity to reply to the comments of Drs Baer and Blumgart relating to my Case Report of probable venous air embolism (VAE). Their letter raises an interesting issue regarding optimum positioning for hepatic surgery.

A head-up tilt has the advantage of providing excellent surgical access to the liver and, with appropriate volume loading to counter postural hypotension, should maintain positive hepatic venous pressures and make passive VAE unlikely. However, any air that does entrain passes readily to the right atrium and, if sufficient, produces pulmonary hypertension and allows paradoxical systemic air embolism in event of a patent foramen ovale. Furthermore, systemic air is more likely to gain access to the innominate and carotid arteries with head-up tilt, inviting cerebral arterial gas embolism.

Venous capacitance vessels are located predominantly in the pelvic and lower limb structures and consequently a head-down position increases central venous pressure as measured with a right atrial catheter. The liver lies in plane similar to that of the heart in this position, with its major veins draining into the inferior vena cava just below the right atrium, so it may be that mean hepatic venous pressure also increases with head-down tilt compared with horizontal or head-up positioning. This should protect against VAE and any bubbles that might be entrained should float caudally in a large-bore, low-pressure vessel such as the inferior vena cava. The disadvantages of head-down attitude include less satisfactory surgical exposure with venous congestion and bowel tending to invade the field and increased right atrial pressures perhaps tending to open a patent foramen ovale, with obvious risks if air were to reach the right atrium.

Current recommendations for management of cerebral arterial gas embolism advocate horizontal rather than head-down posturing. Bubbles are thought to accumulate anteriorly in the aortic outflow tract and not enter the major neck vessels and the adverse consequences of cerebral venous congestion are avoided.

The approximate 30° head-up tilt in the case reported was certainly greater than usual in our community, where positioning varies from horizontal to about 15° head-up, according to surgical preference. As far as I am aware, no specialist hepatobiliary surgeons here use a head-down tilt.

The matter is clearly controversial and may remain dictated largely by surgical considerations. On balance, I feel that the horizontal position offers the best compromise, but concede that the experience of Drs Baer and Blumgart validates their preference for the head-down posture. Head-up tilt would seem the most dangerous option, even though the operative site is nominally below the heart, and I agree with your correspondents that it should be discouraged.

In conclusion, however, I must reiterate the purpose of my article in drawing attention to the need for addressing the potential of VAE in association with the water jet dissector. The incident reported involved dramatic air entrainment of proportions unlikely to be of passive nature, and the warning to anaesthetists remains serious.

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SPIN LABEL TECHNIQUES FOR DETECTION OF MALIGNANT HYPERTHERMIA

Sir,—The differences in the results obtained by Ohnishi and colleagues [1], Halsall, Ellis and Knowles [2] and Cooper and colleagues [3] may not be solely the result of technical factors relating to EPR spectra, as suggested by Halsall, Ellis and Knowles [4].

It is unclear from the paper by Ohnishi and colleagues [1] which sodium phosphate salt was used. They referred to sodium phosphate (presumably Na$_3$PO$_4$). Halsall, Ellis and Knowles [2] have used sodium dihydrogen phosphate. The first invariably requires correction to pH 7.4. It is unclear what effect this has on the availability of the other salts in the buffers.

Calcium has been shown to affect both protein and lipid [5] structure in erythrocytes. Both the incubation and wash buffers used by Halsall, Ellis and Knowles [2] contained calcium.

Methods involving lipid membrane labels usually involve a short incubation period, allowing interpolation of the membrane probe in the bilayer associated with evaporation (or dilution) of the solvent. Alternatively, exchange from Bovine Serum Albumen (also with a short incubation period) can be used. Ohnishi and colleagues [1] and Halsall, Ellis and Knowles [2] used a prolonged incubation period—a technique more akin to protein labelling experiments. Prolonged exposure to some buffers can lead to the loss of membrane constituents [6].

The paper [7] quoted by Halsall, Ellis and Knowles [2] to support the statement that EPR probes do not perturb membranes used samples other than erythrocytes (erythrocytes are unusual in having a large lipid: cholesterol ratio—with obvious implications for changes in fluidity). In addition, the paper did not compare labelled with unlabelled samples or use different label concentrations. EPR probes have been shown to cause morphological changes in erythrocytes [8, 9]. However, the relationship between morphological changes and EPR spectra is unclear [9].

The nature of any differences in erythrocytes between malignant hyperthermia susceptible and normal humans is unclear. Whether it is a primary difference in fluidity remains to be established.

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British Journal of Anaesthesia 1993; 71: 923–925

BOOK REVIEWS

Problems in Obstetric Anaesthetics. Analysis and Management. By A. Rubin and M. Wood. Published by Butterworth-Heinemann Ltd, Oxford. Pp. 138; indexed; illustrated. Price £12.95.

What to include and what to exclude from a small volume on problems in obstetric anaesthesia is a difficult dilemma. Many of the problems encountered in obstetrics are similar to those encountered in other fields of anaesthetic practice (such as anaphylactoid reactions), but have effects on two patients simultaneously. Doctors Rubin and Wood, have sensibly chosen to include these, so that the anaesthetic trainee has the basic groundwork covered for common emergencies. Although it is uncommon, I wonder if malignant hyperpyrexia should have been included, because triggering agents are routinely used for general anaesthesia for Caesarian section?

The book is divided into four sections: co-existing disease, regional anaesthesia in obstetrics, emergencies and a miscellaneous section covering pre-eclampsia, anaesthesia during pregnancy, awareness and abnormal labour and delivery. There are two useful appendices: the physiological changes of pregnancy and drugs used in obstetric anaesthetic practice. I would have wished to see a third, covering drugs safe to use in the breast-feeding mother.

There are several useful tables which enable the trainee to assimilate information quickly. I particularly liked that outlining the course of neurological damage after labour under extradural analgesia.

Problems I would have liked to see mentioned are for how long post-partum does the mother remain at risk of aspiration; if one decides to convert an inadequate extradural block for Caesarean section to a spinal block, what is the appropriate dose of drug to use?; when is uterine relaxation useful at Caesarean section and how is it achieved with an awake patient?; disseminated intravascular coagulation and its management.

An unreferenced text often provides interesting information which one would like to follow up—I was unaware that pre-eclampsia, placental abruption, induced labour and peripartum haemorrhage are more likely to occur in the epileptic parturient.

Although this book is aimed primarily at the anaesthetic trainee, I think midwives would also find the clear and basic information helpful in their understanding of anaesthetic problems in obstetrics.

G. M. Cooper

Differential Diagnosis of Acute Pain by Body Region. Edited by S. L. Wiener. Published by McGraw-Hill Inc., New York. Pp. 845+xlii; indexed; illustrated. Price £49.00.

This is a fascinating book. The editor states that it is designed and written to make the differential diagnosis of acute pain in any region easier, faster and more thorough. He then goes on to say that it is not another volume on pain management designed to deal with the less than 1% of patients who suffer from severe, difficult to control, chronic pain.

With two mistakes in the first paragraph of the book, was the remainder going to be as liberally laced with such gems? No; further delving into the small text in which the book is printed more than justified the effort, for here was a veritable goldmine of disease incidence, symptomatology, differential diagnosis and therapy.

The 10 parts of the book, divided into 51 chapters, cover the various anatomical regions of the body and the many types of pain occurring therein. There is something for everyone, from acute generalized pain to acute scrotal pain, not even missing out the consultant omphalologist, with chapter 20 dealing with acute umbilical pain, albeit in five pages.

For those with an aesthetic bent, the text is preceded by 30 pages of line drawings illustrating the exact area of the body dealt with by each chapter. Although initially appearing somewhat bizarre, these become of increasing value as the reader progresses through the text and are eventually revealed as an indispensable part. It may, however, have been a little easier for the reader had the relevant diagrams preceded each specific chapter, rather than being gathered together at the commencement of the volume.

Each chapter contains not only a detailed description of each pathological entity producing pain in that region, but also a table of disease incidence, so that the likelihood of experiencing each condition can be appreciated and the prevalence per 100000 population is delineated.

In addition to the causes of pain, in some cases an indication of treatment is given which, in some, is quite comprehensive.

Each chapter is extremely well referenced, such that any aspect of the text can be explored at the reader's leisure. The general index is also comprehensive and well cross-referenced.

To whom, then, should this book appeal and be of value sufficient to warrant spending £49?

The editor suggests that primary care physicians in internal medicine and family practice, emergency physicians, medical and surgical residents and medical students should find this book helpful because they encounter every day many patients with pain as a symptom of disease. In fact, any person who deals with the sick and suffering will find this book indispensible. Whilst it is not something that every doctor should purchase, all libraries and educational establishments should ensure that a copy is available, for this is information rarely found in such a form elsewhere. Most practising physicians would benefit by perusing the text, irrespective of their specialty. Those who deal with pain and its ramifications will be especially interested and illuminated by the plethora of information contained in this concise and well constructed book.

Of course, it is easy to be critical of such a work. However, any who criticize should first attempt to put together even one chapter of such an undertaking. Dr Wiener and his colleagues must be congratulated for constructing such a comprehensive and intriguing volume. If only they could have emulated early editions of Lee and Atkinson and included footnotes of historical values in order that the background of such shadowy figures as Eagle, Lachman and Meckel, to name but three, might be elucidated for the education of all. Nonetheless, those who do not expose themselves to this book will miss a treat indeed and be the poorer for so doing. Those who dig into their pockets for the price of this gem will be well rewarded and have on their bookshelves a tome into which they will dip time and time again, always finding something new, edifying and worthwhile.

K. Budd

Manual of Cardiac Anaesthesia, 2nd Edn. Edited by S. J. Thomas and J. L. Crammer. Published (1993) by Churchill Livingstone, Edinburgh. Pp. 591; indexed; illustrated. Price £52.50.

This is a new edition of the previously well received *Manual of Cardiac Anaesthesia.* This is a well written and well organized book in an attractive style which typifies the wry humour of the senior editor. This is evident from his foreword.

The format of the book is its great merit, with a general introduction and each topic divided and subdivided in tabular form.

This is particulary useful in the opening new chapters on Cardiac Physiology and Cardiac Monitoring, in which a plethora of capital letters describing a variety of variables is made clearer than in many other standard works.

The chapters on Congenital Heart Disease and Pacemakers maintain this high standard, also shared by the chapter on Anaesthetic Pharmacology in which, however, it is obvious that this is an American text book, with the occurrence of drug names such as Epinephrine and Meperidine, a discussion of the merits of Sufentinal and a full description of Amrinone as the PDE III inhibitor of choice, with barely a mention of Milrinone and to the total exclusion of Enoximone. An error also occurs in this chapter, in which the medium effective dose of Epinephrine is stated to be "2 micro litres per kilogramme".

The manual states didactically the ideas of the authors; however, it is sometimes difficult to find the facts upon which these are based, for references are not given and it is necessary to guess the appropriate reference from the list of suggested reading.

Nonetheless, these criticisms are minor and although the work is seen as a reference book for the trainee anaesthetist and the working anaesthetist, it will repay attention from a much wider audience.

D. G. Lewis

Resuscitation Handbook, 2nd Edn. Edited by P. J. F. Baskett. Published by Mosby Year Book Europe, Aylesford, Kent. Pp. 136; indexed; illustrated. Price £14.95.

In this second edition, 4 years after the first, Dr Baskett has revised the text and illustrations to incorporate the latest European Resuscitation Council and American Heart Association guidelines. There are now six sections, a new Paediatric section contributes 10 of the additional 18 pages, and an expanded, up-to-date bibliography. However, it remains a concise manual with the same clever use of colour to enhance illustrations or to emphasize important points.

The introductory section discusses the causes and outcome of cardiorespiratory arrest, with a clear "decision not to resuscitate algorithm", and the infective hazards of resuscitation.

The second section has 62 pages, divided into life support during resuscitation and restoration of the spontaneous heart beat. The use of the laryngeal mask, the Pharyngo Tracheal Lumen Airway, percutaneous dilatational cricothyrotomy and active compression decompression is discussed comprehensively and illustrated. In restoration of the spontaneous heart beat, arrhythmias, defibrillation and drug therapy are described. The 10 pages of resuscitation algorithms follow the European Resuscitation Council guidelines.

The third section on Trauma Life Support (32 pages) describes the Primary Survey, Restoration of Vital Functions and Secondary Survey according to the 1992 ATLS guidelines. Multi-lumen catheters, the Level One Infusion Device, the radiology of spinal injury and the Interosseous Screw are now included.

The fourth section on Paediatric Resuscitation by Dr David Zideman is completely new. Descriptions of basic and advanced techniques for airway management, breathing and circulation are followed by a discussion on vascular access, fluid administration and drug therapy.

The fifth section has 5 pages on the effective relief of pain in all emergency situations. Finally, the tables on training requirements now include use of the laryngeal mask by all groups except the lay public and rescue services!

It is interesting to note that the individuals now wear gloves for most invasive procedures, but not all illustrations have been revised. The layout of the text has been slightly altered in this edition and, unfortunately, the descriptions have sometimes become separated from the diagrams or tables. I feel that adenosine should have been included in the Paroxysmal Supraventricular Tachycardia algorithm.

There is no comparable manual which provides so much data in a compact, interesting and readable format, which can be used by all those involved in resuscitation at all levels of expertise. This handbook states the current practice of resuscitation and should be essential reading for medical students, paramedics, nurses and all doctors.

T. M. O'Carroll

Baillière's Clinical Anaesthesiology: *Anaesthesia and the Geriatric Patient*. Edited by C. Dodds. Published by Baillière-Tindall, London. Pp. 198; indexed. Price £27.50.

Virtually all anaesthetists are involved in providing safe anaesthesia for the increasing numbers of elderly patients in their care. The aim of this book is to update and refresh the knowledge of the reader in this area. It has been 5 years since the last edition in this series was devoted to the elderly patient.

The opening chapter in this book is a thought-provoking account written by The Right Reverend Lord Bishop of Durham D. E. Jenkins, on the ethics of caring for the elderly. He discusses in depth the ethical and philosophical issues concerned with the use of medical techniques to prolong life, and the relevant areas of priorities and rationing of scarce health care resources. The reader is challenged to address these difficult and demanding areas.

The following chapter is concerned with the ageing process and the demography of the ageing population. Theories of the mechanism of ageing are discussed, as are the differences that exist in body composition between the young and old. I found the section in this chapter on the pharmacodynamics of drugs used in the elderly very useful.

Cardiopulmonary physiology and changes in the elderly are covered comprehensively in the next chapter. This includes sections on the control of breathing and cardiovascular control.

One aspect of the perioperative management of the elderly patient that is of importance is control and maintenance of body temperature; this is clearly discussed in the subsequent chapter. The next few chapters are allocated to the discussion of the management of the elderly patient undergoing surgery, including day-case surgery and minimally invasive surgery.

I found the chapters on anaesthesia for vascular surgery and urological surgery both relevant and readable, each chapter being well referenced. The final two chapters in this book concern the postoperative period, immediate postoperative management and postoperative pain control in the elderly.

As with many other texts in this series, I found this book clinically useful. I have no doubt that many anaesthetists will find it to be of great value.

J. A. Langton

Orthopedic Anesthesia. Edited by D. J. Wedel. Published by Churchill-Livingstone, Edinburgh. Pp. 441; indexed; illustrated. Price £55.00.

There have been enormous advances in orthopaedic surgery in recent years with the development of knee, elbow, shoulder and hand arthroplasty, and the wide application of arthroscopic techniques to many joints. Coupled with these has been an increasing willingness, on the part of anaesthetists, to accept for major procedures patients who, not so long ago, would have been considered unfit for anaesthesia of even the most minor type. As the population itself ages, the demand for orthopaedic operations grows and so not only the scope of the subspecialty expands, but also the volume. Patients' expectations have also increased, fuelled by both the media and the so-called Patient's Charter and there is a relentless demand for more procedures to be performed on a day-case basis. Many patients now expect to be involved in the choice of anaesthetic technique and some feel it is their right to refuse a particular method. Many are led to believe that a pain-free recovery phase is guaranteed.

These are exciting challenges for orthopaedic anaesthetists and have triggered refinements of established techniques and the adoption of some new ones. That this should prompt a specialist text is a reflection of the extent to which orthopaedic anaesthesia has become a subspecialty in its own right.

This book has been written by a group of 14 anaesthetists from the Mayo Clinic. An effort has been made to limit the number of authors, with several, including the editor, contributing more than one chapter. Both elective orthopaedics and fracture surgery are covered, together with some topics which would not usually fall inside the ambit of orthopaedics in the British Isles, for example microvascular surgery, chronic pain. The book does not appear to have been written specifically for those in training and this may, at least partly, explain its curious layout.

The main problem with the book is that, although there is plenty of information, it is scattered in the chapters on preoperative evaluation, transfusion medicine, coagulation problems, comparison of regional and general anaesthesia, positioning and monitoring, complications and postoperative pain management. The reader will have to work very hard indeed to extract those parts of each of these which might be relevant to the management of, for example, total knee replacement or arthroscopic meniscectomy. Paradoxically, there are some chapters on anaesthesia for specific procedures—spinal surgery (prolapsed disc and corrective operations taken together), orthopaedic tumours and microvascular surgery. The emphasis in some of these, particularly that on orthopaedic tumours, can only be described as bizarre. Here the reader is given a description of 37 different types of bone tumour, from enchondroma to adamantinoma and varieties of sarcoma (six pages). This is followed by an encyclopaedic section on the pharmacology of chemotherapeutic agents for use in bone cancers, ranging from nitrogen mustards to dactinomycin and cytarabine—in all, nearly 40 different drugs (seven pages). There is then a short section on radiotherapy which includes a table of the minimal toxic doses of radiotherapy for the larynx, lung, liver and other tissues. The anaesthetic management of patients with bone tumours finally rounds off the chapter in little more than three pages, nearly 50% of which are concerned with monitoring, blood loss and positioning—topics which are already considered under their own chapter headings.

There are many gaps and not a few inconsistencies. Although the use of an extradural blood patch for treating post-dural puncture headache is mentioned on several occasions the reader is left guessing as to the specific indications for this. To write that "The successful use of spinal anesthesia necessitates the early use of epidural blood patching when indicated" is hardly helpful. There are no details of how this procedure is performed (there is a statement that 15 ml of blood is effective) or if, and how often, it can usefully be repeated.

There is no mention of the use of intra-articular opioids or local anaesthetics for postoperative pain relief after arthroscopic meniscectomy. The authors do not consider the particular anaesthetic problems of bilateral knee joint replacement, an operation which is occasionally necessary to assist postoperative mobilization. Similarly, the anaesthetic management of patients undergoing repair of the anterior cruciate ligament and the problem of providing effective pain relief for this very painful operation are not addressed.

Neither droperidol nor ondansetron are mentioned as treatments for opioid-induced nausea and vomiting and there is virtually no information on vasopressors such as ephedrine, phenylephrine or methoxamine for the management of hypotension during spinal or extradural block. The use of prophylactic antibiotics before implantation of foreign materials is also ignored. These latter omissions are the more inexplicable given the emphasis on other less relevant aspects.

In the evaluation of patients with ischaemic heart disease (p. 7), the authors suggest that "A good history will identify most patients." They do not indicate those circumstances when routine electrocardiography is mandatory and they do not mention that this investigation is the single best predictor of outcome after non-cardiac surgery. Instead, there is a long theoretical description of "Stress Radionuclide Perfusion Imaging" which fails to address a most important question—in which patients should it be undertaken? The emphasis is, again, peculiar given the importance which the authors, quite rightly, attach to the medical history compared with the "less efficient and more expensive laboratory tests". They go on to state that "In the healthy patient undergoing elective or emergency surgery, no 'routine' laboratory evaluation is required". This is surely bad advice, from both a clinical and a medico-legal point of view. How else is the orthopaedic anaesthetist to identify incipient chronic renal failure, for example? What about bedside urinalysis as a simple and inexpensive screen for diabetes mellitus and a midstream specimen of urine to exclude urinary tract infection in the elderly? It would also seem foolish (perhaps negligent) not to check the haemoglobin concentration and white cell count before joint replacement, particularly when blood will have been taken for cross-matching. The authors do not mention cardiac pacemakers or any of the potential problems associated with their use.

Despite these reservations, there is much about this book which is good, indeed excellent. In particular, the chapters on transfusion medicine, patient positioning, spinal and extradural blocks, peripheral nerve blocks, outpatient surgery and postoperative analgesia are brimming with useful information and good diagrams. The chapters are well referenced, although the number of British references is very small.

There are a few typographical errors. Perhaps the most glaring is the misprinted header on the odd pages 3–13, reading incorrectly as "positioning and monitoring" instead of "preoperative evaluation". Other minor errors which caught my eye included "mivicurium" (pp. 244, 429), "Korttilla" (p. 254 refs 54, 55), "Kortilla" (p. 254 ref 51), "MacKensie" (p. 253 ref. 26), and "Girodano" (p. 53 ref 205). An index in a book on orthopaedic anaesthesia which lists *Adamantinoma, characteristics and treatment of*, and *Minnesota Multiphasic Personality Inventory*, but not *Arthroscopy*, or *Extradural blood patch* would seem to have the wrong emphasis. The book is well produced in a good quality hardback cover.

J. P. H. Fee

ERRATUM

British Journal of Anaesthesia 1993; 71: 326–327

The name of a co-author, R. Ginsburgh, was inadvertently omitted from authorship of the letter entitled "Haemodynamic effects of propofol".

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